

STUDIES IN THE DEVELOPMENT  
OF EXPERIMENTAL PHARMACOLOGY  
IN THE EIGHTEENTH AND EARLY NINETEENTH CENTURIES

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### ABSTRACT

General pharmacology in the seventeenth and eighteenth centuries is considered (Parts 1 and 2). Reference is made to some criticisms of the contemporary materia medica and to early attempts at a scientific investigation of drugs and poisons. The studies of vegetable drugs by Stoerk and Withering are discussed to illustrate the problems associated with pharmaco-dynamic studies in clinical practice.

Part 3 describes the experiments with drugs and poisons carried out in the eighteenth century. Particular reference is made to experimental studies of cherry laurel, arrow-poisons, viper venom and opium. The influence of this work on the history of experimental pharmacology is considered in a discussion concerning the recognition of animal experiments as a valid contribution to pharmacology and human medicine.

In Part 4 the factors contributing to advances in posology are discussed with particular reference to experimental studies and to the isolation of active constituents of drugs. Part 5 is concerned with the development of knowledge concerning the mode of action of drugs and poisons, in particular with the problem of the manner in

which a substance can affect an organ situated at a distance from the site of administration. These sections of the thesis include a study of the work of some investigators in the early nineteenth century with particular reference to some early researches by François Magendie.

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Plates II, II, IV and VIII are by courtesy of the  
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Plate VII is by courtesy of the Science Museum Library.

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## INTRODUCTION

A number of physicians in the seventeenth and eighteenth centuries, influenced by developments in experimental science, began to take a more critical view of the large collection of real and supposed remedies then in common use. The gradual rationalization of the materia medica that followed, resulted in the simplification of the eighteenth-century pharmacopoeias and the deletion of superstitious and traditional remedies. Deletion, however, is a negative process and this rejection of the inert, when once initiated by more rational modes of thought, required little more than experience and common sense to accomplish it. The study of the active materials on the other hand demanded more positive and objective methods of approach.

In the late seventeenth century attempts were made to define and predict medicinal action by a study of the sensory, botanical and chemical characteristics of drugs. These methods, although achieving a limited success with some drugs, did not yield the results necessary to establish a reliable therapeutic or pharmacodynamic classification, and still less lead to a knowledge of the mode of action. The two principal sources of

information leading to such a knowledge are (i) objective experimentation on animals and (ii) clinical practice. In the eighteenth century the greater care and precision that developed in clinical practice gave rise, in a few cases, to more objective reporting of the effects of drugs, but this source did not contribute greatly to knowledge concerning pharmacodynamic action. The best known examples are the studies by Anton Freiher: von Stoerk with hemlock, stramonium, aconite and colchicum, and William Withering's study of digitalis. It must be remembered, however, that in these excellent studies the reporting of pharmacodynamic effects was secondary to the therapeutic purpose of the work which was directed to the relief of certain symptoms. Likewise many animal experiments carried out during this period were undertaken with therapy in mind. Here, however, because the observations were made on healthy animals, the results were more productive of a knowledge of the true pharmacological effects of the substances investigated. In this thesis a number of these animal experiments have been studied in order to show that, although they were primarily made for therapeutic, toxicological or physiological purposes, they were none the less concerned with some problems of pharmacology and might, therefore, be rightly considered as part of the history of that subject.

It is necessary at this point to give some consideration to what is meant by pharmacology since its exact meaning has changed over the years and even today is variably defined. The word is derived from the Greek Pharmakon - a remedy. John Schroeder in his Pharmacopoeia Medico-chymica (Lugduni, 1649) used the term Pharmacologia and William Rowland in an English edition (London, 1669) translated this into Pharmacology. Rowland described pharmacology as "the Art of making Medicines" and later in Nathaniel Bailey's An Universal Etymological English Dictionary (London, 1721), it is defined as a "Treatise concerning the Art of Preparing Medicines". The word subsequently assumed a much wider meaning. Jonathon Pereira in his textbook on the materia medica, first published in 1839, defined pharmacology as a branch of therapeutics devoted to a consideration of medicines. He divided the subject into pharmacognosia, the study of crude drugs, pharmacy, the preparation and dispensing of medicines, and pharmaco-dynamics, which treats of the effects and uses of medicines. A number of modern medical and general dictionaries continue to define the word as "the science of the effects of drugs" but in Germany and in the English-speaking world this definition is no longer exact. In the latter half of

the nineteenth century Rudolf Buchheim and his pupil Oswald Schmiedeberg of the University of Dorpat freed pharmacology from traditional therapeutics so that substances were grouped according to their chemical nature and pharmacodynamic action instead of their therapeutic effects. The modern pharmacology which has developed from this movement is, therefore, more accurately defined as the experimental investigation of the action of natural and synthetic substances on healthy animal tissues. It is not wholly concerned with the effects of medicinal substances; and, where these are investigated, the term applied pharmacology is more appropriate, or pharmacotherapeutics, if the investigation is made on diseased tissue. In this thesis, which is concerned with the seventeenth, eighteenth and early nineteenth centuries, the word pharmacology is used in its older sense, i.e. synonymous with materia medica, and the term experimental pharmacology is used to represent the experimental investigation of medicines and poisons on living animals with the object of discovering their effects and mode of action.

The following studies in the history of pharmacology begin with developments in the latter half of the seventeenth century when the need for a scientific



evaluation of the materia medica was acknowledged. They are concerned with related aspects of general and experimental pharmacology during the eighteenth and early nineteenth centuries and attention is specifically drawn to the resolution of three problems: first, the recognition of animal experiments as a valid method for the investigation of substances intended for human medicine; secondly, the conception of 'dose' and the application of this factor; and finally, the problem of the mode of action of drugs with reference to their absorption and the manner in which they affect an organ situated at a distance from the site of administration.

During the period under review a great many drugs and poisons were investigated by feeding or injecting them into the bodies of animals, but the majority contributed little to the solution of the above problems. This was because only a small number of experiments were carried out in each case and crude and uncontrolled methods were used. The main contribution is to be found in the work associated with a relatively small number of substances and particular reference has been made to these. They include, opium, cherry-laurel water, curare and strychnine arrow poisons, viper venom, and some vegetable drugs in particular hemlock, digitalis and nux vomica. Work

carried out with these substances involved planned experiments and reproducible techniques, at first on the crude materials and later on the isolated active constituents, i.e., morphine from opium, hydrocyanic acid from cherry-laurel and strychnine from nux vomica.

The studies end in the nineteenth century with the early work of the physiologist, François Magendie, a founder of modern pharmacology, who as early as 1817 anticipated the benefits to mankind that would follow the physiological investigation of "cette foule de corps simples ou composés que la chimie nous révèle chaque jour".

## 1. DEVELOPMENTS IN PHARMACOLOGY DURING THE SEVENTEENTH CENTURY

### (i) Materia Medica and Therapeutics

The seventeenth century was a period of therapeutic credulity. The greater proportion of the simples and preparations were included in the official pharmacopoeias on little more than the recommendation of their traditional use in medicine. Their presence in earlier authoritative works and their long continued use in general practice had bestowed upon them a firm, although largely undefined, therapeutic reputation.

#### (a) The origins of the materia medica

The materia medica was of Graeco-Arabic origin. The first 'official' pharmacopoeias, published during the fifteenth and sixteenth centuries in Italy and Germany, were based on classical and Arabic medical literature, supplemented by mediaeval compilations and commentaries. Valerius Cordus (1515-1564) used the works of Galen (A.D. ca. 129-200), the works of Dioscorides (1st cent.A.D.) and mediaeval formularies compiled from Arabic sources for his Dispensatorium (1546), the official pharmacopoeia of Nuremberg.<sup>1</sup> Of the thirty-one animals listed in the

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<sup>1</sup>. Huseman, T. Introductory Essay to the Augsburg Pharmacopoeia, Madison, 1927, p. xi.

Catalogus simplicium of the Pharmacopoeia Londinensis (1618), twenty-one appear in the works of Dioscorides. In the same work eighteen pharmaceutical preparations are derived from Galen, four from Avicenna (980-1037) and eight from Rhazes (865-925); forty-nine preparations are taken from the Salernitan Antidotaries (12th and 13th cent.) which were collections of Greek, Latin and Arabic recipes and one hundred and sixty-six are attributed to the Grabadin of Mesuë junior.<sup>2, 3</sup> To these Graeco-Arabic medicines there were added many indigenous remedies originating in European folk-lore and indigenous plant remedies contributed by the herbalists. European medical literature added new compound remedies to the materia medica, a few original, the majority variations of older

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<sup>2</sup> Urdang, G. History of the Pharmacopoeia Londinensis, Madison, 1944, pp. 37, 67, 69.

The facts given refer to the second issue of the first edition of the London Pharmacopoeia (December 1618). The first issue (May 1618) was suppressed.

<sup>3</sup> The Grabadin of Mesuë junior, Mesuë the Younger or pseudo-Mesuë is now generally believed to be a compilation from Arabic sources written in Italy during the thirteenth century. The adoption by the author or authors of the name Mesuë illustrates the prestige of Arabic medicine.

see Urdang, G. op. cit., p. 71; Sarton, G. Introduction to the History of Science, Baltimore, 1931, vol. 2, p.854.

recipes. Among the contributors of compounded medicines were Arnald of Villanova (c. 1235-1311), Allesandro Benedetti (d. 1525), Pietro Andrea Matthioli (1500-1547), Girolamo Fracastoro (1478-1553) and Jean Fernel (1499-1558).<sup>4</sup>

The number of 'approved' remedies increased in the seventeenth century as a result of the entry into official therapy of the chemical or 'spagyric' medicines. The spagyrics (Gk. Span: to separate; ageirein: to combine) were introduced by Paracelsus (1493-1541) and they were the first serious challenge to traditional Graeco-Arabic therapy. They were specific, active chemical salts and plant extracts many of them having a powerful and rapid effect on administration in sharp contrast to the milder effects of the 'Galenical' remedies which were simple admixtures of crude drugs often compounded with a number of inert materials. The use of the chemical remedies formed the basis for a bitter medical controversy during the latter part of the sixteenth century. The opposition was founded on the authority of the traditional Graeco-Arabic works and supported by the obvious toxicity of the

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<sup>4</sup> Huseman, T. op. cit. p. xl.  
Urdang, G. op. cit. p. 68.

more favoured chemicals, notably antimonial and mercurial salts. The first official recognition of chemiotherapy was given in the sixth edition of the Pharmacopoeia Augustana (1613) edited by the eclectic Raymund Minderer (1570-1621), although it was in Augsburg in 1582 that the Senate had, by decree, banned the use, preparation and sale of spag<sup>y</sup>ric remedies. Further recognition was given in the London Pharmacopoeia of 1618 through the influence of Sir Theodore Turquet de Mayerne (1573-1655), a paracelsist persecuted for his views by the University of Paris in the years before he settled in England.<sup>5</sup>

The recognition of chemical remedies, although an advance in therapy, had the effect of adding more materials to a materia medica to which there had been already too many additions and too few deletions. The seventeenth-century materia medica is characterized by its size, the wide variation in the nature of its constituent remedies and the large number of inactive materials it contained. In the first edition of the Pharmacopoeia Londinensis there were 1,190 vegetable, animal and mineral substances listed in the catalogus simplicium. The list included 292 Herbae et carum Folia (herbs and

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<sup>5</sup> Urdang, G. Archives Internationales D'Histoire Des Sciences. 1954, ~~Numero 28-29~~, 303-314.

their leaves), 138 Radices (roots), 31 Animalia (animals), 25 Marina (marine products) and 73 Metallica et Mineralia (metals and minerals). In addition to the simples there were 963 compounded remedies ranging from simple distilled waters to electuaries with over one hundred ingredients. The collection exhibited a wide range of activity ranging from the highly active and toxic materials (opium, nuxvomica and soluble mercurials) through reasonably and mildly effective evacuant, alterative and dietetic materials down to the inert and therapeutically valueless. The latter class is a characteristic of the materia medica of the seventeenth century. A number of the vegetable remedies were little more than flavouring or colouring agents whilst a large number of the animal and mineral products possessed neither therapeutic nor pharmaceutical properties. The Pharmacopoeia Londinensis, (1618), for example, included Catuli (puppies), Lustra (otter), Adeps Pardi (grease of panther), Stercus Humanum, Lupinum ..... (Excreta of man, wolf and nine other species), Lapis Bezoar (Bezoar stone), Opalus (Opal), Sapphirus (sapphire) and other similar materials, many of them originating in the ancient doctrines of sympathy and signatures.

Treatment of disease was largely empirical and

involved the excessive use of purges, emetics, diaphoretics and phlebotomy. This treatment was in accord with the prevailing doctrine of humoral pathology which had originated in the Hippocratic school. The doctrine, as elaborated by Galen, postulated that disease was the result of an excess of one or more of the four humours of the body and the object of therapy was to evacuate the excess humours to restore the equilibrium on which health depends. This was accomplished by evacuant medicines, purges, emetics, etc., the choice of which depended upon the associated 'qualities'. Each humour was associated with two 'qualities' (see Plate 1) and remedies were chosen having 'qualities' opposite to those possessed by the humour to be evacuated. John Woodall in The Surgeons Mate (London, 1639) described Senna leaves as being:

'..... hot and drie in nature, they are an excellent medicanent for purging the belly; it Scoureth away flegmaticke, tough, and melancholy humours from the braine, lungs, spleene, liver, stomacke and bowels.' (p. 64)

The wide application of the humoral pathology brought about a rough classification of drugs and preparations according to their evacuant properties and



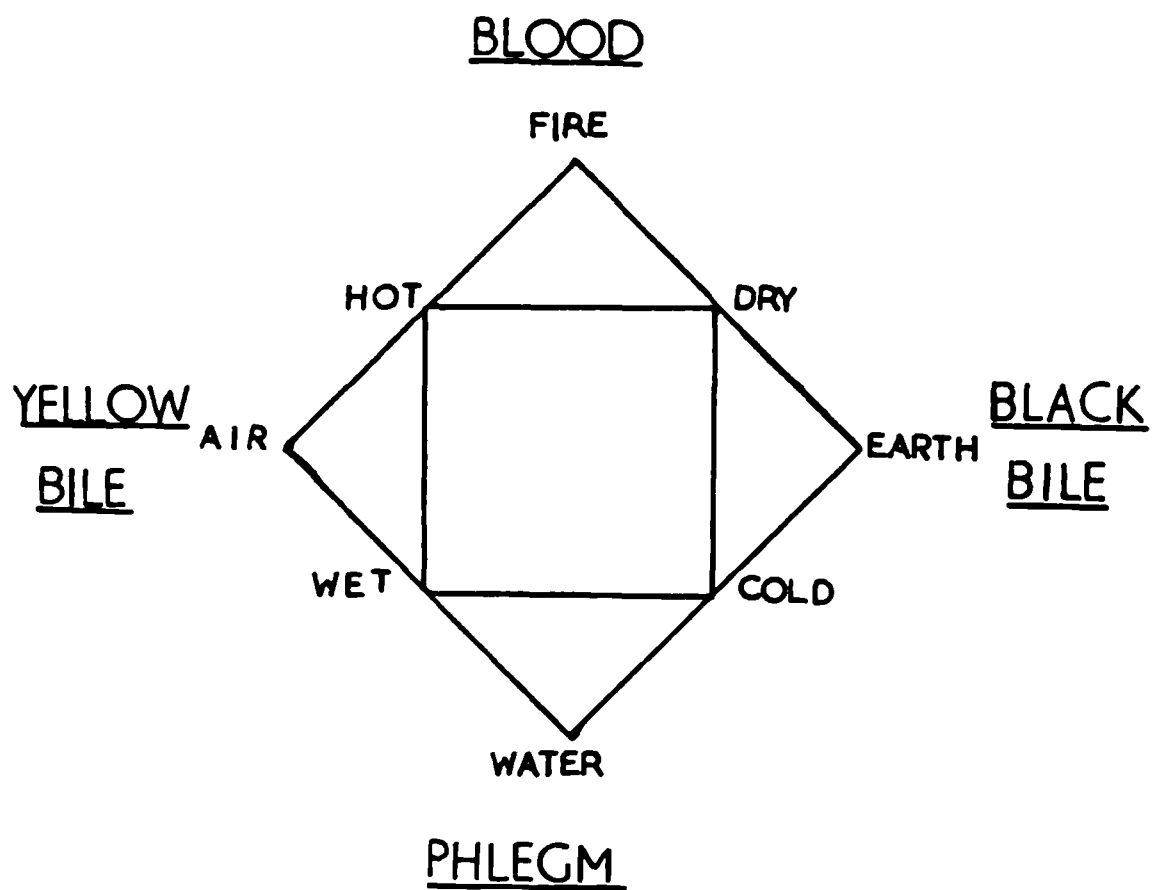


Plate I. The elements, qualities & humours.

the terms Vomit, Purgative, Diuretic, Sudorific and so on were commonly used to describe medicines. Where a substance was found to be effective in a particular condition without an apparent evacuation it was generally described as a 'Specific'. This classification represents the limit of knowledge concerning the action of drugs at the beginning of the seventeenth century. Further advance in pharmacodynamics was restricted first, by the influence of dogmatic medicine and the unquestioning allegiance of physicians in all levels of practice to the doctrines of folk medicine and the authoritative and traditional works; second, by the difficulties associated with the study of drug action during the course of clinical practice - the only source of pharmacological knowledge before the advent of experimental studies.

(b) The influence of dogmatic medicine

Irrational practices originating in folk medicine and from Graeco-Arabic sources persisted longer in the materia medica than in any other branch of medicine. The iatrochemical and iatrophysical doctrines and the advances in physiology during the sixteenth and seventeenth centuries had but little influence on practice in general and therapy in particular. The advances

in science had no immediate application to the problems facing the physician in his day-to-day practice and the leaders of the iatrochemical school themselves did not abandon the older remedies in their practice. Sylvius (1614-72) frequently prescribed galcnical remedies<sup>6</sup> and Thomas Willis (1621-1675) recommended the ancient panaceas Theriaca and Mithridate and items such as 'Powder of Toads' and 'Salt of Vipers'.<sup>7</sup>

The power of dogmatic medicine on the materia medica is manifest in the Galenist-Spagyrist controversy following the introduction of chemical remedies into medicine. In the early seventeenth century, in those countries where chemicotherapy had received a measure of recognition, its advocates were careful to pay due respect to traditional therapy. In the preface to the Pharmacopoeia Londinensis (1618) de Mayerne writes:

"Although we revere the wisdom of the old masters and have arrayed their preparations, so to speak, in the first line of battle, nevertheless we

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<sup>6</sup> Meyer-Steineg & Sudhof, Geschichte der Medizin, Jena, 1950, p. 318.

<sup>7</sup> Willis, T. Pharmaceutice rationalis; or, an exercitation of the operation of medicines in humane bodies, London, 1679, Part I, pp. 51, 123.

have not rejected or distained in this book the auxiliary troops of the new chemistry, but have granted them a place, a corner in the rear guard, so as to have them at the disposal of dogmatic medicine, i.e. ready for serving like auxiliaries".<sup>8</sup>

This traditionalism not only served to support and maintain Greco-Arabic materia medica, it led also to opposition to new specific remedies, in particular Peruvian bark (cinchona) introduced into Europe in 1632.<sup>9</sup> Few changes are to be seen in the pharmacopoeias until just before the middle of the eighteenth century.

(c) The study of the action of drugs in clinical practice.

Clinical experience cannot be regarded as a precise and exact method of pharmacological study beset, as it is, with so many varying factors. In the seventeenth century, although the need for care and the possibility of error did not go unrecognised,<sup>10, 11</sup> medical

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<sup>8</sup> from the English translation by G. Urdang, History of the Pharmacopoeia Londinensis, Madison, 1944, p. 30.

<sup>9</sup> Castiglioni, A., A History of Medicine, New York, 1947, p. 559.

<sup>10</sup> Sydenham, T. Preface to Observationes Medicae circa Morborum acutorum Historiam et Curationem, in Opera Universa, London, 1685.

practice was a source of fallacious remedies and false conclusions. A limited knowledge of the nature and progress of disease, ignorance of natural healing processes and a disregard for the need to verify observations led to many erroneous reports on the action and therapeutic value of medicinals. Thomas Sydenham (1624-1672), whose principal achievement was to draw attention to the importance of a careful study of the nature of disease, reported that physicians were often deceived into mistaking one disease for another, and to such errors he attributed the existence of many valueless remedies.<sup>12</sup> Later Cullen<sup>13</sup> described how during this period remedies were reported to be of value in dysentery when in fact they had only relieved simple diarrhoea and Lewis<sup>14</sup> rebuked earlier physicians for careless and arbitrary reports written "as if diseases of the same parts, or of the same name were always of the same nature

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<sup>11</sup> Dodard, D, Mém. Acad. R. Sci., 1666-99, (pub. Paris, 1731), 4, pp. 452, 526.

<sup>12</sup> Sydenham, T., Observations Medicae, Preface.

<sup>13</sup> Cullen, W., A Treatise of the Materia Medica, Edinburgh, 1789, Vol. 1, p. 145.

<sup>14</sup> Lewis, W., An Experimental History of the Materia Medica, London, 1761, p.v.

or were always to be treated by the same remedies".

To the errors arising out of a lack of definition of the pathological conditions of the subjects treated, there must be added those originating in the difficulties inherent in pharmaceutical practice. The seventeenth century was an age of polypharmacy; drugs were rarely administered alone but were invariably mixed with a number of other substances some active others inert. Treatment was not uniform, several different types of preparation being given over a relatively short period. Dosage was variable and, if the action of a preparation was correctly observed, the specific effects were not always attributed to the correct ingredient. Under these conditions, it was very easy for physicians to assume that recovery or apparent recovery attributable to natural processes was due to the administration of their 'favourite' prescription.

(ii) Criticisms of the Materia Medica in the Seventeenth Century.

In the seventeenth century there was increasing criticism of the materia medica and a loss of confidence in the therapeutic value of many of its constituents. This criticism, which came from both physicians and laymen, was often coupled with a demand for a rational approach to the study of the effects of drugs.

Francis Bacon (1561-1626) in the Advancement of Learning (1605) complained of the reliance placed on panaceas by contemporary physicians and their neglect of remedies for specific diseases. Medicine he described as being "more professed than laboured and yet more laboured than advanced". Sydenham<sup>15</sup> described the materia medica as a large collection of remedies of little value to the sick and Willis condemned the fortuitous administration of medicines:

"For certainly the not duly weighing the Reasons by which Medicines operate, renders all Physic to be Empirical, and to be governed rather by Chance or Fortune than by Advice." <sup>16</sup>

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<sup>15</sup> Sydenham, T., Observations Medicae, Preface.

<sup>16</sup> Willis, T., Pharmaceutice Rationalis, London, 1684, Part II, Preface.

Robert Boyle<sup>17</sup> (1627-1691) attacked the doctrine of humours as a basis for therapy and he was followed later by Giorgio Baglivi<sup>18</sup> (1668-1707) who showed that some remedies, contrary to the doctrine, cured diseases with which they had 'qualities' in common.

Two suggestions for a rational approach to the study of the action of drugs were associated with the growing appreciation of irrational elements in the materia medica. The first was directed to practicing physicians and indicated that rational and effective treatments would result from careful observation and verification of results. Sydenham wrote that the method of improving medicine consisted in

"..... delivering a fixed and every way complete method of cure; such a one .... as hath been sufficiently establish'd and verified by a competent number of experiments, and found effectual to cure any particular disease. For I conceive it is not enough to publish the particular success of any method or medicine, if

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<sup>17</sup> Boyle, T., Considerations touching the Usefulness of Experimental Naturall Philosophy, Oxford, 1664 (2nd edit.), part 2, p. 277.

<sup>18</sup> Baglivi, G., De Praxis Medica, Lugduni, 1699, p. 267.



neither are generally found to answer the end  
in all cases, at least in the same given  
circumstances." 19

The second was directed to understanding the modus operandi of drugs in order to predict their effects following administration and this was expressed by John Locke (1632-1704) in the Essay Concerning Humane Understanding (1690)

" Did we know the mechanical affections of the particles of rhubarb, hemlock, opium, and a man, as a watchmaker does those of a watch, whereby it performs its operations, and of a file, which by rubbing on them will alter the figure of any of the wheels, we should be able to tell beforehand that rhubarb will purge, hemlock kill, and opium make a man sleep: as well as a watchmaker can that a little piece of paper laid on the balance will keep the watch from going till it be removed; or that, some small part of it being rubbed by a file, the machine would quite lose its motion and

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19 Sydenham, T., Works, trans. by John Swan, London, 1749, p. xii.

the watch go no more."

(Book IV, Chap. iii, 25)

The clearest exposition of the two types of investigation believed to be necessary for the understanding of the action of medicines was given by Baglivi. The first, that leading to verified treatments, he believed to be within the scope of all physicians. They must

" ..... consult the Oracles of the Senses, and the Observations made upon the Juvanta or Loedentia, or the Event of Remedies; and draw upon from thence Cautions and Standing Precepts, relating to the Use, Quantity, Time, and other Conditions of Remedies".<sup>20</sup>

The second, from which resulted a knowledge of the operation of medicines, is one of greater difficulty and Baglivi believed it to require co-operative effort and a wide knowledge of science:

"..... this [operation of remedies] is a very deep Point, and lies at the remotest

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<sup>20</sup> Baglivi, G., De Praxis Medica, Lugduni, 1699. Taken from the English translation entitled The Practice of Physic, London, 1704, p. 324.

Distance from the Senses, 'tis the Business  
not of one Man, but of a whole Society of  
Physicians: For to illustrate that subject  
theres a necessity of taking in Many things  
from Chymistry, from the Mechanicks, from  
Anatomy, the Principles of natural and  
experimental Philosophy, etc." <sup>21</sup>

(iii) Development of Methods for the Investigation of  
Drugs and Poisons.

During the seventeenth century three general  
methods for the investigation of drugs and poisons were  
developed. They were:

one, the determination of medicinal effects of  
vegetable drugs by reference to morphological features  
(natural-historical qualities) or to sensory characters.

two, the study of drugs and poisons by means  
of chemical analysis, and

three, the study of pharmacological and toxi-  
cological action (pharmacodynamics) by means of experi-  
ments on living animals.

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<sup>21</sup> Ibid., p. 334

(a) Determination of effects by reference to morphological and sensory characters.

This method was essentially one of classification and arose from the ancient and natural assumption that plants possessing common characteristics of structure or similar sensory characters will have the same medicinal properties. The earliest affirmation of the existence of affinities between botanical structure and medicinal effect is attributed to Andrea Cesalpino (1519-1603) <sup>22</sup> although the first clear exposition of the principle was possibly the dissertation De convenientia Plantarum in fructificatione et viribus by Rudolph Jacob Camerarius (1665-1721) published at Tübingen in 1699. <sup>23</sup> In the eighteenth century the theory was supported in works by Linnaeus, <sup>24</sup> Gmelin, <sup>25</sup> Isenflamm, <sup>26</sup> and Wilcke. <sup>27</sup>

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<sup>22</sup> Dierbach, J.H., Abhandlung über die Arzneikräfte der Pflanzen, Lemgo, 1831, p. 1.

<sup>23</sup> De Candolle, A.P., Essai sur les Propriétés Médicales des Plantes, Paris, 1816, p. 4.

<sup>24</sup> Linnaeus, C., Vires Plantarum, Resp. F. Hasselquist, Upsala, 1747, in Amoenitates Academicae, Erlangae, 1787, Vol 1, p. 418.

<sup>25</sup> Gmelin, P., Botanica et chemia ad medicam applicata proxin per illustria quaedam exempla, Tübingen, 1755.

Opposition to the theory was based on the very obvious exceptions to the rule that plants of the same class possess similar medicinal virtues.<sup>28, 29</sup> This opposition was dealt with in the early nineteenth century by De Candolle who made a careful survey of all known exceptions and tried to explain them away. He gave eight possible causes for the existence of exceptions to the theory which included explanations such as variations in botanical classification and inadequate observations on the effects of the drugs.<sup>30</sup> Although this theory had proved to be of little practical value, De Candolle's work prolonged its life and as late as 1849 the pharmacologist Pereira was not prepared to reject it absolutely although he admits that "in the present state of Science botanical affinities cannot be confidently relied on by the medical practitioner for

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<sup>26</sup> Isenflamm, J., Methodus plantarum medicinae clinicae adminiculum, Erlangae, 1764.

<sup>27</sup> Wilcke, H., De usu systematis sexualis in medicina, Resp. H.A. Rosenthal, Gryphiswaldiae, 1764.

<sup>28</sup> Lewis, W., Materia Medica, London, 1761, p. vi.

<sup>29</sup> Cullen, W., Materia Medica, Edinburgh, 1789, vol i., p. 135.

<sup>30</sup> De Candolle, A.P., Essai ..., Paris, 1816, pp. 371-2.

determining the effects of remedial agents".<sup>31</sup>

The sensory characters of colour, taste and odour which are natural features for distinguishing substances either as food or physic, were also used as a means of classifying the therapeutic activities of vegetable materials. Sir John Floyer (1649-1734)<sup>32</sup> attempted to found a system of *materia medica* by relating sensory characters to the known action of plant drugs. Later Linnaeus<sup>33</sup> supervised attempts to relate the action of drugs to their taste and smell. Although the idea engaged the attention of several writers, the weakness of an investigation based on subjective phenomena was soon realised. In a paper to the Royal Society in 1720 Patrick Blair<sup>34</sup> (fl.1728) pointed out the variations in sensations of taste that occur between

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<sup>31</sup> Pereira, J., The Elements of Materia Medica and Therapeutics, London, 1849, vol. 1, p. 84.

<sup>32</sup> Floyer, Sir J., Pharmako-Basanos: or the Touchstone of Medicines, London, 1687.

<sup>33</sup> Linnaeus, C., Sapor Medicamentorum, Resp. J. Rudberg, Upsalia, 1751 in Amoenitates Academicae, Erlangae, 1787, vol ii, p. 365.

Linnaeus, C., Odores Medicamentorum, Resp. A. Wählin, Upsalia, 1752, in Amoen. Acad., Erlangae, 1787, vol. iii, 183.

<sup>34</sup> Blair, P., Phil. Trans., 1720, 31, 30.

individuals. Cullen,<sup>35</sup> although he believed that only drugs with an odour and taste were active, rejected the sensory characters as being of any assistance in the investigation of drugs and he severely criticised the work of Floyer, Linnaeus and others in favour of the theory. He believed such investigations to be misleading <sup>owing</sup> ~~due~~ to the difficulties in determining tastes and classifying odours. The absence of a simple relationship existing between sensory characters and pharmacological action was evident after the discovery and extraction of the active principles of vegetable drugs. Pereira,<sup>36</sup> to illustrate this, compares the difference in activity between Quinine and Strychnine both of which are intensely bitter.

(b) The study of drugs and poisons by chemical analysis

The chemical investigation of drugs was first seriously applied in the seventeenth century when the chemicotherapeutic movement, initiated by Paracelsus, had received some measure of official recognition and when the iatrochemists were applying chemical doctrines to medicine and physiology.

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<sup>35</sup> Cullen, W., Materia Medica, Edinburgh, 1789, vol. i pp. 26, 138-142.

<sup>36</sup> Pereira, J., London Medical Gazette, 1836, 17, 2.

The basis of therapy according to the doctrine of four humours was that the effectiveness of a remedy depended upon its possession of certain qualities opposite to those associated with the condition it was intended to cure. The iatrochemists substituted for these qualities the chemical properties of acid and alkali which led to a consideration of other chemical properties associated with a known remedy. There arose the belief that chemical analysis of vegetable, mineral and animal drugs would lead to a knowledge of their mode of action and relate activity to particular constituent parts.

"..... there is little doubt but such Tryals  
[analysis of vegetable drugs] will make them  
discover, to a considering Naturalist, much of  
their Nature and Properties, and especially of  
such as depend chiefly upon the plenty or paucity  
of the Saline, unctuous, sowre, spiritous, lazy,  
tenacious or volatile Parts." 37

The chemical analysis of plants as a means of studying their 'virtues' was carried out by members of

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37 Boyle, R., Experimental Naturall Philosophy, Oxford, 1664, part 2, p. 116.



L'Académie Royale Des Sciences, Paris. Du Clos<sup>38</sup> in 1668 drew attention to possible chemical explanations of therapeutic effects and of the value of chemical analysis as a method of study. A very large number of plant analyses followed largely the achievement of Bourdelin<sup>39</sup> and Dodart, and a discussion of the work appears in the Memoires pour servir a l'Histoire des Plantes.<sup>40</sup>

The value of this form of study was soon in question. The crude methods of analysis used, i.e. destructive distillation, resulted in the same 'chemical' products being obtained from a culinary vegetable as from a known plant poison<sup>41</sup> and the realisation of this brought about a rejection of 'analysis by fire' <sup>42, 43</sup> and the use, in its place, of milder methods of analysis

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<sup>38</sup> Hist. Acad. R. Sci. 1666-1686, (pub. 1733)  
1, 37.

<sup>39</sup> Ibid., 2, 16.

<sup>40</sup> Dodart, D., Mem. Acad. R. Sci., 1666-1699, (pub. 1731)  
4, 120.

<sup>41</sup> Homberg, G., ibid., 1701 (pub: 1743), 115.

<sup>42</sup> Lemery, N., ibid., 1719, (pub. 1721),  
173.

<sup>43</sup> Boulduc, G., ibid., 1734, (pub. 1736), 101.

in particular the pharmaceutical methods of extraction by decoction and infusion.<sup>44</sup> Chemical analysis continued to be regarded a valuable means of investigation of drugs throughout the eighteenth century until, towards the end, the idea that pharmacological activity could be determined by chemical studies alone was abandoned. Cullen expressed this in 1789:

".... wether the medicinal virtue be found to reside in a volatile or a fixed, in a gummy or resinous part, it will still require and depend upon experience to determine what its virtue is." <sup>45</sup>

(iv) Experimental Pharmacology in the Seventeenth Century.

The third method of drug investigation to develop in the seventeenth century was the experimental study of the action of drugs on living animals. The method was not new. Since earliest times experiments had been conducted using slaves, animals and condemned criminals and the literature of toxicology cites many examples of the effects of poisons and medicines

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<sup>44</sup> Cullen, W., Materia Medica, Edinburgh, 1789, vol i, p. 28.

<sup>45</sup> Ibid., vol. i, p. 28.

administered by way of experiment. Attalus III of Pergamon experimented with poisons and antidotes on condemned criminals and Locusta is reported to have used slaves and animals to test the effect of her poisons. Experiments with animals are referred to by Shakespeare in Cymbeline.

Queen: Now, Master doctor, have you brought those drugs?

.....

I will try the forces  
Of these thy compounds on such creatures as  
We count not the worth of hanging, - but none  
human, -  
To try the vigour of them and apply  
Allayments to their act, and by them gather  
Their several virtues and effects.

(Act I, Sc. 5)

In Rome in 1524 and later in Prague in 1561, condemned criminals were given the root of napellus (*Aconitum napellus*) as an experiment<sup>46</sup> and many similar cases could be cited. Most of the cases concern poisons either as a means of discovering their efficiency or as a test for some supposed antidote. Relatively few experiments

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<sup>46</sup> Matthioli, P.A., Commentarii, in libros sex Pedacii Dioscoridis anazarbei, de Medica Materia, Venice, 1565, p. 1096.

concern known remedies, one example being the treatment of quartan fever with opium by Fallopius (1523-1562); the subject, a criminal given over to the physician by the Grand Duke of Tuscany, died after the second experiment.<sup>47</sup>

In the seventeenth century the use of living men for such experiments was rare although it was still seriously considered as a possible method of study. The use of animals on the other hand increased towards the end of the period and there was the beginning of an attempt<sup>to</sup> standardise and control experiments.  
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The experimental study of the effects of remedies and poisons on living animals was suggested by Francis Bacon in the New Atlantis (1627) where he writes of enclosures where birds and animals might be kept for this purpose as well as for physiological and surgical studies. The method of experimenting with living animals to demonstrate physiological truths was put into effect by William Harvey (1578-1657) in his work on the circulation. Unfortunately the use of animals to demonstrate the action of drugs and poisons was beset with certain difficulties which suggested that pharmacological

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<sup>47</sup> Astruc, J., De Morbis Venereis, Paris, 1740, Vol. 2, pp. 748-749.

experiments with animals would not be comparative. It was a well known fact that some animals are immune to plants known to be poisonous to man: pigs, sheep and goats, for example, can eat large quantities of Deadly Nightshade (Atropa belladonna L.) without visible harm. This problem, although it was used as an argument against comparative studies in pharmacology for many years, was seen by some seventeenth-century authors to be limited to a relatively small number of poisons. Boyle<sup>48</sup> comments that the greater number of poisons are toxic to both man and beasts and goes on to say that experiments with animals "allows us great opportunities of observing their manner of operation and investigating their Nature ...". Later Richard Mead<sup>49</sup> (1673-1754) observed that, although with plants there was a range of possible effects between man and animals, the mineral poisons are "universally hurtful and destructive".

In the seventeenth century experiments using living animals were mostly toxicological and, although the majority of substances studied were included in the

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<sup>48</sup> Boyle, R., Experimental Naturall Philosophy, Oxford, 1664, part 2, p. 48.

<sup>49</sup> Mead, R., A Mechanical Account of Poisons in Several Essays, London, 1702, p. 101.

materia medica, the results of the experiments did little more than demonstrate or confirm their poisonous properties. Experiments with recognised therapeutic agents were limited to their administration by the newly discovered method of injection into the veins and to their use in a condition which could be artificially introduced into the healthy animal. Boyle suggests that the remedies which may be investigated by animal experiments are antidotes for poisoning and remedies for the cure of wounds, it being relatively simple to poison or wound an experimental animal.<sup>50</sup>

In the early work many different species were used for these experiments. The members of the Royal Society investigated the effects of poisons on birds<sup>51</sup> and amphibia.<sup>52</sup> John Jacob Wepfer (1620-1695) experimented with the wolf, fox, species of birds, dogs and cats.<sup>53</sup> Boyle suggested dogs and monkeys as animals most suitable for this work.<sup>54</sup>

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<sup>50</sup> Boyle, R., Experimental Naturall Philosophy, Oxford, 1664, part 2, 232.

<sup>51</sup> Birch, T., History of the Royal Society, London, 1756, vol i, p. 29.

<sup>52</sup> Ibid., vol. i, pp. 231, 234.

<sup>53</sup> Wepfer, J.J., Cicutae Aquaticae Historia et Noxae, Basle, 1679, pp. 153, 170, 244, 235.

The general method of experiment was to feed the substance to be studied to the animal in its food or to force it down the throat. In some cases the poison was inserted into a wound. Another method, developed during the latter half of the seventeenth century, was direct injection into the blood by means of an incision in a vein. This method arose directly from the work of Harvey on the circulation. The first to infuse drugs into the vein of an animal was Christopher Wren (1632-1723) at Oxford in 1656. His first experiments were on dogs using opium and the purgative crocus metallorum (impure oxysulphide of antimony) and the technique was to ligature an exposed vein and inject the substance through an opening in the vessel by means of a quill to which a bladder was attached.<sup>55</sup> The further study of this method was pursued by Timothy Clarke (d. 1672) who, in 1662, after a request by members of the Royal Society for a communication on the results of his experiments, described the injection of infusions of senna and agaric into the veins of dogs.<sup>56</sup> Clarke's

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<sup>54</sup> Boyle, R., Experimental Naturall Philosophy, Oxford, 1664, part 2, p. 232.

<sup>55</sup> Oldenburg, H., Phil. Trans., 1665, 1, 128.

<sup>56</sup> Birch, T., History .... vol. i, pp. 25, 80.

work was followed by that of Major,<sup>57</sup> Fracassatus<sup>58</sup> and Elsholz<sup>59</sup> (see Plate II). The principal interest in intravenous injection at this time was in its therapeutic possibilities and the first tests were carried out using opiates, purges and emetics. Later there arose the suggestion of administering foods in this way and in 1666, in the course of a discussion on blood transfusion, Boyle and others suggested the possibility of injecting broth, milk and other liquid diets.<sup>60</sup> The first experiment with intravenous injection on man was carried out by Boyle in 1657 using a purgative drug<sup>61</sup> and was repeated later by others including Dr. Vincent Fabricius who injected purgative drugs into three of his patients.<sup>62</sup> The obvious dangers attendant on this technique, which soon became apparent, together with the difficulties of administration, did not recommend it to general medical practice and in some countries the method was banned as a means of treating man. Nevertheless, it continued to

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<sup>57</sup> Major, J.D., Chirurgia Infusoria, Kiel, 1667.

<sup>58</sup> Fracassatus, C., Phil. Trans., 1667, 2, 490.

<sup>59</sup> Elsholz, J.S., Clysmatica Nova, Berlin, 1665-1667.

<sup>60</sup> Birch, T., History ..., vol. ii, pp. 84, 134.

<sup>61</sup> Boyle, R., Experimental Naturall Philosophy, Oxford, 1664, part 2, p. 55.





CLYSMATICA NOVA. In  
 lionem curvitas potius, quam adju-  
 vat. Hinc frustulo fungi orbicularis  
 imposito, curem acia confui, atque  
 ita canem in terram reposui. Ipse  
 lambere vulnus horam mediam,  
 mox surgere, & fugam quasi nihil  
 passus, arripere.

*Explicatio literarum in Fig. 1.*  
 qua depingitur

### Infusio simplex in brutis.

- a. Vena cranialis, in Canis dextra.  
 b. Sypho liquore medicato repletus, & vena  
 scissa insertus.  
 c. Manus Chirurgi sinistra, vaginam tenens.  
 d. Manus Chirurgi dextra, si apum impellens.  
 e. Manus ministri, digito venam comprimens.

Hac igitur ratione certior redditus, 1. Per vi-  
 immissionem istam non tantum innum.  
 cadavere fieri posse, quemadmodum  
 in brachio suffocata mulieris à me su-  
 perius fuit ostensum, sed etiam in  
 vivente: tentavi idem in secundo  
 cane, ea tamen differentia, ut loco  
 sim-

Plate II. Injection into the vein of a dog.

From Elsholz, Clysmatica Nova, 1667.

be used for experimental purposes on animals and is associated with subsequent studies with drugs and poisons.

The first recorded series of experiments with living animals to observe the effects of a poison are those carried out by Thuillier, physician to the Duke of Sully, in 1630. Thuillier fed Ergot of Rye (Claviceps purpurea) to farmyard animals and showed it to be the cause of the gangrenous disease ignis sacer (ergotism), then epidemic among the French peasantry. This work was reported by his son to Dodard, when the latter visited the area to investigate the outbreaks of the disease.<sup>63</sup>

Experiments with poisons appear among the earliest experiments of the Rôyal Society. In 1661 the attention of members was drawn to the doses of nux vomica and sublimate of mercury required to kill various species of birds.<sup>64</sup> In April 1665 the members began a study of the 'Florentine poison' (Oil of Tobacco) at the request of Charles II. The poison, which is obtained by the distillation of tobacco leaves, was administered to cats, dogs and pullets by mouth, injection into wounds and

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<sup>62</sup> Fabricius, V., Phil. Trans., 1667, 2, 564.

<sup>63</sup> Dodard, D., J. des Scavans, 1676, reprinted Amsterdam, 1683, p. 81.

<sup>64</sup> Birch, T., History ....., vol. i, p. 29.

injection directly into the veins. They observed the rapid and fatal effects when placed on the tongue of a kitten and the symptoms of vomiting, stupor and convulsions which occurred in larger animals. This series of experiments came to an end in June 1665 when the Society discontinued its meetings on account of the plague.<sup>65</sup> Interest in this virulent poison was shown by others at this time and experiments with it were carried out by Courten, Harder (vide infra) and Nicolas Lemery (1645-1715) who injected the oil under the skin of a dog and recorded the symptoms of poisoning.<sup>66</sup>

Toxicological and pharmacological studies during this period were little more than a series of miscellaneous experiments administering selected materials and simply noting the more obvious symptoms. The work carried out by William Courten (1642-1702) is characteristic of the period. Courten's experiments with poisons were made at Montpellier between 1678 and 1679 and the results were communicated to the Royal Society of London by his friend, Hans Sloane, Secretary of the Society.<sup>67</sup> The report of the work consists of a

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<sup>65</sup> Birch, T., History ..., vol. 2, pp. 31-57.

<sup>66</sup> Lemery, N., Cours de Chymie, Paris, 1677, p. 528.

<sup>67</sup> Courten, W., Phil. Trans., 1712, 27, 485.

miscellany of toxicological and physiological experiments which include administration of poisons by mouth and by injection, experiments with poisonous animals including vipers and scorpions and experiments to observe the effects of cutting certain nerves. Several of the experiments with poisons are inconclusive, for example the plant poisons solanum (atropa belladonna), cicuta (hemlock), wolfbane (aconite), helleborus albus (veratrum albi) and colchicum emphemerum (colchicum autumnale L.) were all administered in turn to the same dog either as the whole plant or as the juice expressed from the leaves. No observable effects were noted for the first four poisons but with the colchicum the animal was 'violently tortured'.<sup>68</sup> Courten does not comment on the results of these experiments. The work with tobacco was more exact and the injection of a decoction of tobacco leaves into the crural vein of a dog was repeated on several occasions, in each case giving rise to convulsions which the author described as 'strange'.<sup>69</sup> It is possible that these 'strange' convulsions were the cramp-like spasms of nicotine poisoning. The

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<sup>68</sup> Courten, W., Phil. Trans., 1712, 27, 485-486.

<sup>69</sup> Ibid., 498.

experiments with opium, then one of the most widely used items in the materia medica, did little to increase the knowledge of its action. In the first experiment, carried out in 1678, two drachms (120 grains) of the drug was administered to a dog by mouth and the resulting narcotic effects are described. The animal recovered ~~due~~<sup>owing</sup> to the fact that it vomited some of the opium<sup>70</sup> (a more successful experiment was conducted later in England by Richard Mead who showed that, using this dose, the period of narcosis is followed by convulsions and death<sup>71</sup>). In his second and third experiments with opium (1679), Courten injected one and a half drachms (90 grains) dissolved in one and a half fluid ounces of water into the crural vein of dogs. He noted convulsions followed by narcosis terminating in death.<sup>72</sup> Among other materials injected in these experiments were sal ammoniac, olive oil and white wine. These experiments did little more than demonstrate the dangers of administering materials by this method, as in most cases injection was followed by violent convulsions which ended in the death of the animal. Although Courten

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<sup>70</sup> Courten, W., Phil. Trans., 1712, 27, 486.

<sup>71</sup> Mead, R., Essay on Poisons, London, 1702, p. 141.

<sup>72</sup> Courten, W., Phil. Trans., 1712, 27, 493-494

often carried out post-mortem examinations of the poisoned animals, his findings were not relevant to the experiment and limited to observations on unusual features such as the presence and nature of parasitic worms.

In sharp contrast to the work of Courten, which is characteristic of this period, are the experiments with poisons carried out by John Jacob Wepfer between 1675 and 1679, the results of which are published in the Cicutae aquaticae historia et noxae (Basle, 1678). Wepfer was born at Schaffhausen in 1620. He obtained his Doctor's degree at Basle in 1647 and shortly afterwards he was appointed physician to that city. In 1658 he published his work Observationes anatomice ex cadaveribus eorum quos sustulit apoplexia (Schaffhausen, 1658) wherein he showed the relationship between cerebral haemorrhage and apoplexy a condition which, until that time, had been attributed to many strange and fanciful causes. In the Observationes anatomice Wepfer proved himself a careful, unprejudiced observer, whose work was in the spirit of Vesalius and Harvey. He died in 1695 at the age of seventy-five in the service of <sup>the</sup> Emperor Leopold whose army was, at that time, ravaged by an epidemic fever.<sup>73</sup>

In the Cicutae aquaticae attention is primarily directed to the water hemlock (cicutae aquaticae or cicuta virosa), an umbelliferous plant found growing beside lakes and ponds in Europe. Wepfer recognised the plant as a virulent poison and records several cases of poisoning among children who had eaten the roots in mistake for parsnips.<sup>74</sup> He investigated its toxic properties by feeding the root to dogs and wolves carefully noting symptoms and post-mortem findings. Wepfer extended these experiments to other materials and he investigated the toxic indigenous herbs nappellus (aconitum napellus)<sup>75</sup> and hellebori albi (veratrum albi);<sup>76</sup> items of the materia medica ~~nuxis vomicae~~ nux vomica,<sup>77</sup> amygdalum amarum (bitter almonds),<sup>78</sup> coccularum (cocculus indicus),<sup>79</sup> gialappa (jalap)<sup>80</sup> and the minerals antimony,<sup>81</sup> arsenic,<sup>82</sup> mercury sublimate (mercuric chloride) and mercury dulcis (calomel).<sup>83</sup>

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<sup>73</sup> Eloy, N.F.J., Dictionaire Historique de la Médecine, Mons, 1778, p. 567.

<sup>74</sup> Wepfer, J.J., Cicutae Aquaticae, Basileae, 1679, pp. 5, 80, 107.

<sup>75</sup> Ibid., p. 176.

<sup>80</sup> Ibid., p. 221.

<sup>76</sup> Ibid., p. 219.

<sup>81</sup> Ibid., p. 249.

<sup>77</sup> Ibid., p. 194.

<sup>82</sup> Ibid., p. 278.

<sup>78</sup> Ibid., p. 235.

<sup>83</sup> Ibid., pp. 296-303.

<sup>79</sup> Ibid., p. 184.

Dogs, cats, wolves and birds including pigeons and storks, were used for this work. Each experiment was carefully reported with a description of the subject, time of administration and dose of material used in the experiment. The symptoms following administration were carefully observed and on occasion the animal was vivisected and movement and appearance of internal organs noted. In • nearly all instances post-mortem studies were carried out. Wepfer's report of his first experiment with Nux vomica for example, carefully described the tetanic convulsions of strychnine poisoning and in particular the effects upon the diaphragm. Post-mortem examination revealed no observable changes in the stomach or blood which were the parts of the body believed at that time to be the most affected in cases of poisoning.

"At 2 p.m. on the 16th July, 1676, in the company of the noble D.D. Heinricho Screta à Zavorziz I introduced into a stray puppy about three weeks old, half a drachm 30 grains of powdered Nux vomica mixed with milk. For some time nothing abnormal was noticed except that the puppy whined. After a quarter of an hour had passed, the head was immediately tossed up and down and was drawn from side to side; at times it trembled as if it



was suffering from a rigor, cried continuously and vomited clean uncoagulated milk. Shortly afterwards the animal laid down, first on its belly, then on its back with its feet stretched out stiffly and extended in a true tetany; from time to time the whole body was shaken with convulsive movements and soon the whole body became stiff like a piece of wood and from that time it ceased to whine and the tongue continuously hung from its mouth. The abdomen was greatly swollen. After it had been afflicted with convulsion for two hours and was half dead, I cut the abdomen and during the cutting the dog began to whine again and to be agitated with a convulsive movement which turned at once to a tetany. The stomach, with both openings tightly shut, was distended. When it was cut out, we saw the crura of the diaphragm, before it became fully distended and expanded as in breathing, shaken by a convulsive movement as in sobbing. In the stomach we found clots of milk, a great deal of frothy mucus and bits of straw. When it had been cleaned of the contents, we could see no signs of inflammation although the

ob motum Cordis vel abolitum vel admodum turbatum in vas subsistens grumefactus fuit, aut si qua coagulabatur, nullum tamen valetudini damnum attulisset, quin potius citra alexipharmacorum aliorumve dissolventium usum supervixissent, nisi globus plumbeus cani & Nux vomica caniculae vitam abstulisset.

5. Canicula superato primo acerrimo consistu, minus postea à *cocculis* crebrius & copiose ingestis lædebat, nec tantumultus excitabatur, non quod ventriculus in tam brevi & acerbio tyrocinio veneno affluerit ac ventriculo familiaris redditum fuerit, nec quod ventriculi membrana nervae stupidiore facta adversus injurias *coccularum* induruerit, nam eundem sensum quem prius habuit, retinuit, appetiit, oblata avidè devoravit, sed potius propterea, quia ventriculi tunica mucosa, à mucopos ejus oblinente mundata, permisit, ut spicula *coccularum* citius membranam nerveam ferirent, unde insurgentes fibrae *cocculi* maturè eliminarunt per vomitum & secessum: fortè etiam multum fermenti benignioris in fundo ventriculi aderat, post longa irritamina ex arteriis elicti, quod acrimoniam *coccularum* infregit.



### CAPUT XIII. De Nuce Vomica:

#### Historia I.

**C**aello projectio trium circiter septimanarum, 16. Jul. 1676. limature Nucis Vomicae drachmam dimidiam, hora secunda pomeridiana, cum Nob. D.D. Heinricho Secreta à Zaccharia lacti permixtam infudi. Aliquandiu nihil p. n. observatum fuit, nisi quod vagiret: clapo horæ quadrante caput subinde succuba-

tiebatur, aut in latustrahebatur, aliquando tremuit ac si rigorem patiretur: interea vagiit continuò, evomit lac sincerum, non coagulatum: paulò post nunc pronus, nunc supinus, exporrectis pedibus inflexibilibus, vero tetano extensus, jacuit, quandoque totum corpus motibus convulsivis concutiebatur & multavariè jactabatur, mox toto corpore & collo instar schidii rigidus protensus pedibus evalit, atque ab illo tempore vagire desit, exserta continuè lingua: abdomen valdè intumuit. Postquam duabus horis convulsionibus afflictus jam semimortuus esset, abdomen incidi, intersecandum rursus vagire & motu convulsivo agitari coepit, qui protinus in tetanum vertebatur. Ventriculus, utroque orificio arctissime clauso, supra modum distensus erat; illo exsecto vidimus diaphragmatis crura, antequam illud in inspiratione ad plenam distensionem & expansionem perveniret, motu convulsivo, ut in singultu, succuti. In ventriculo invenimus lac grumofum cum muco spumoso multo & frustulis straminis: illo a contentis mundato, nulla inflammationis signa observare potuimus, anfractuum tamen superficies minus alba erat ac alias conspicitur. Ventriculo exsecto nihilominus artus & collum à tetano rigebant; diaphragma diu & sæpius brevibus intervallis motu convulsivo succutiebatur: ex venis & arteriis sanguis largè, splendide rubescens emanavit nullibique concretus, aut grumofus à nobis vilis fuit. Aperto pectore cor veluti emortuum, cultelli apice irritatum, movebatur subinde. Tertia hora post exhibitam nucem Vomica incisis cordis ventriculis & Venà cavà prodiit sanguis fluxilis, grumorum prorsus expers.

#### II.

Caniculae provectioris ætatis, mediocrius magnitudinis, pilis nigris prædite circa principium Septembris 1677. Cl. D.D. Joh. Conrad. Brunnerus dedit Tartari Emetici grana aliquot, nullo subsequente effectu memorabili, imò quasi nihil hujusmodi affumil-

Bb 2

surface at the bends of the stomach was less white than at other times. After the stomach had been cut out, the limbs and neck remained stiff with the tetany. For a long time the diaphragm was shaken by a convulsive movement which became more frequent. We saw that from the veins and arteries bright red blood flowed freely, and was nowhere congealed or clotted. When the breast was opened, the heart appeared as if dead, but when irritated with the point of a knife it moved. In the third hour after the Nux vomica had been given when, the ventricles of the heart and the Vena cava had been cut, fluid blood issued forth, quite free of clots."

(Cicutae Aquaticae, pp. 194-195,  
see Plate III).

In addition to proving experimentally that the Water hemlock and Nux vomica were convulsive poisons, Wepfer was able to show by post-mortem studies that arsenic and corrosive sublimate, both extensively used in medicine, were violent corrosive substances.

This experimental study of materia medica and known poisons was made more complete by the work

of another Basle physician John Jacob Harder (1656-1711) who held the chairs of Rhetoric (1678), Physic (1686), Anatomy and Botany (1687) and finally theoretical Medicine (1703) at the University of Basle.<sup>84</sup> Between 1680 and 1681 Harder investigated the action of Oil of Tobacco experimenting on a variety of animals including lizards, frogs, snakes, storks and dogs. The results of this work were published in a series of seven 'observations' in the Apiarium Observationibus Medicis centum ac Physicis Experimentis Plurimis refertum ad Scholiis atque Iconibus pulcherimis illustrandum, (Basileae, 1687). Harder also made experiments with Cicutae terrestris or the common hemlock (*Conium maculatum*), the effects of which Wepfer had not studied in detail. Harder communicated the results of the hemlock experiments to Wepfer in 1684 and the care shown in the work is similar to that of the older physician. Harder administered the expressed juice of the plant to dogs, by mouth and by injection into the jugular vein.<sup>85</sup> In both the hemlock and the tobacco-oil experiments symptoms of poisoning are described together with post-mortem findings.

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<sup>84</sup> Biographie Médicale, Paris, 1822, vol. 5, p. 74.

<sup>85</sup> Harder, J.J., Apiarium, Basileae, 1687, pp. 106-110.

By the end of the seventeenth century the method of experimenting with animals to study the effects of poisons and items of materia medica had been developed. Although the majority of recorded experiments at this time differ but little from the experiments on men and beasts which appear in toxicological literature since the earliest times, certain improvements in experimental technique are evident. To the method of administering the substances by mouth or by rubbing into open wounds there was now the technique of direct administration into the circulation by means of intravenous infusion. Attention to dose is evident in the work of Courten, Harder and Wepfer and the post-mortem studies of the latter directed attention to the fact that changes in body organs and fluids are as important as symptoms and manner of death which were the principal features of earlier experiments.

The actual results arising from these innovations in method were very few at this time. Infusion into the vein although carried out successfully in a number of experiments was limited in value due to lack of knowledge concerning the necessary properties of materials most suited for injection. This lack of discrimination in the substances injected not only

brought about a rejection of the method in therapy it also gave rise to a large number of valueless investigations such as the experiments of injecting quantities of crude mercury into the veins of dogs.<sup>86, 87</sup> The value of an increased care in dosage was limited by the variable nature of the preparations used, particularly vegetable drugs and poisons. With such materials only the extreme effects of large doses were exactly reproducible. Similarly post-mortem studies at this time only revealed the more obvious features of tissue damage such as corrosion or acute inflammation. Some time was to elapse, therefore, before the methods adopted in the seventeenth century became exact techniques in controlled experiments.

(v) Knowledge and Theories Concerning the Mode of Action of Drugs and Poisons.

At the close of the seventeenth century it was generally accepted that, for a generalised action on the body, medicines and poisons must first enter the circulation. This belief followed from the discovery

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<sup>86</sup> Moulin, A., Phil. Trans., 1690-1, 17, 436.

<sup>87</sup> Pitt, C., ibid., 1698, 20, 185.

of the circulation of the blood by William Harvey who referred to this mode of action when he explained why certain medicines, applied externally, exert their power internally as if they had been administered by mouth.<sup>88</sup>

Later Boyle, suggesting the external application of medicines as an experimental procedure, directed the substance to be applied to the animal in those parts "where the vessels that convey Blood more approach the surface of the Body".<sup>89</sup> Again in his discussion of specifics, Boyle states that these substances behave in the same way as poisons and gain "access to the mass of Blood - which is very easily done by the circulation".<sup>90</sup>

Willis likewise believed medicines to enter the blood and opiates, for example, were carried in the blood to the brain where they "do exert their drowsie Quality".<sup>91</sup> The knowledge that medicines and aliments enter the circulation was the cause of the seventeenth-century

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<sup>88</sup> Harvey, W., Movement of the Heart and Blood in Animals. Trans. by K. J. Franklin, Oxford, 1957, p. 93.

<sup>89</sup> Boyle, R. Experimental Naturall Philosophy, Oxford, 1664, part 2, p. 51.

<sup>90</sup> ibid., p. 262.

<sup>91</sup> Willis, T., Pharmaceutice Rationalis, London, 1684, part 1, p. 126.

enthusiasm concerning the therapeutic possibilities of direct infusion of drugs and nutriments into the blood through the veins.

The effect following this absorption was at this time beginning to be related to the dose administered. Willis, discussing emetics, writes:

"As to what some affirm, To Wit, That a Vomit, be it given in a Dose never so great, works no stronger than if it were taken in a small quantity, is altogether false, and a thing not to be experimented without a great deal of danger." <sup>92</sup>

Wepfer, Harder and Courten, as we have seen, carefully recorded the doses of the poison administered in their experiments. Baglivi suggested that the effects from a certain dose might be varied according to the site of administration. He reached this conclusion after experiments conducted at Naples in 1693 when he injected two fluid ounces of rectified spirit of wine (alcohol) into the veins of dogs. He observed that alcohol injected into the jugular vein killed the dog,

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<sup>92</sup> Willis, T., Pharmaceutice Rationalis, London, 1684, part 1, p. 22.



whereas when injected into the crural vein it only brought about convulsions from which the animal recovered. Baglivi believed that the fatal effects of the spirit was due to its power to coagulate the blood and he explained the result of his experiments by saying that the coagulating property of the alcohol, when injected into a vessel remote from the heart and lungs, is reduced (by dilution) before it reached the larger blood channels.<sup>93</sup>

The idea of a specific action upon a particular organ or at a particular site had been expressed at this time although only in vague terms and then only associated with a small number of substances. For some time before the seventeenth century medicines had been designated in a way so as to suggest action on a specific organ for example hepatics (action on the liver) and cordials (action on the heart). These medicines were believed to have an affinity or 'sympathy' with the affected organ and, when this idea was questioned and largely rejected in the seventeenth century<sup>94</sup>, the possibility of specific

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<sup>93</sup> Baglivi, G., De Praxi Medica, Lugduni, 1699, pp. 389-392.

<sup>94</sup> Boyle, R., Of the Reconcilableness of Specifick Medicines to the Corpuscular Philosophy, London, 1685, p. 72.

action at a particular site was transferred to a small group of relatively new drugs whose action could not be explained by evacuation of morbid materials. These were the 'specifics' which Willis defined as Medicines "which are given to cure either some peculiar Diseases, or which are said to respect some Region or part of the Body".<sup>95</sup>

Sydenham's idea of a specific was limited to a drug having the property of curing a particular disease and he recognised only one true form - the Peruvian bark (Quinine bark or cinchona) used for the treatment of fever. He rejected other recognised specifics on the grounds that they cured by evacuation; mercurials, for example, brought about a salivation which he believed to be a form of evacuation.<sup>96</sup> Boyle believed the action of these materials was due to their specific effect upon particular parts and organs and explained their virtues at some length in the second part of his work Some Considerations Touching the Usefulness of Experimental Naturall Philosophy (1663), and again later in Of the Reconcilableness of Specifick Medicines to the Corpuscular Philosophy (1685). At the time Boyle was

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<sup>95</sup> Willis, T. Pharmaceutice Rationalis, London, 1684, part 1, Preface.

<sup>96</sup> Sydenham, T., Works, London, 1749, p. xviii.

writing the use of specifics in medicine was a major point of controversy among physicians and Boyle's reasoned arguments in favour of these medicines are in marked contrast to that strange collection of superstitious and credulous remedies he published under the title Medicinal Experiments: or a Collection of Choice and Safe Remedies (1692).

The seventeenth century saw the development of mechanical-chemical explanations of drug action which stemmed from the theories of the iatromechanists and iatro-chemists. Willis, leader of the iatrochemical school in England, attributed the action of diaphoretics to particles of the medicine which enter and ferment the blood <sup>97</sup> and of emetics to their disturbing the 'animal spirits'. Willis actually experimented with emetics injecting antimony in wine into the jugular vein of a dog. He reached the conclusion that the emetic acted upon the brain and that vomiting in this case arose from the same cause as vomiting following a head injury; in both cases the animal spirits

"being disturbed excite the others that

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<sup>97</sup> Willis, T., Pharmaceutrice Rationalis, London, 1684, part 1, p. 85.

inhabit the Stomach into the same commotion,  
by the commerces or intercourse of the eighth  
pair of nerves." <sup>98</sup>

The action of opiates Willis attributed to the presence of sulphurous particles united with a fixed salt which then carried to the brain overpower the subtle and volatile animal spirits.<sup>99</sup> Richard Mead similarly ascribed the action of opium to its sulphurous particles although he believed the action not to be on the brain but directly on the stomach:

"the opium by lightly Rarefying the Juices of the Stomach, and causing a pleasant Titillation of its Nervous Coate, will induce an agreeable Plentitude, and entertain the Mind with Ideas of Satisfaction and Delight." <sup>100</sup>

Boyle explained the action of specifics in his first work on the subject by a system of filters and ferments at the site of action. The tissues of the

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<sup>98</sup> Willis, T., Pharmaceutice Rationalis, London, 1684, part 1, pp. 13, 22

<sup>99</sup> ibid., p. 126.

<sup>100</sup> Mead, R., Essays on Poisons, London, 1702, p. 137.

organ were said to constitute the strainer or filter which, combined with a ferment, changed the size, motion and shape of the medicinal particle, giving rise to a specific action on the organ concerned.<sup>101</sup> In a later work, however, Boyle explains that *this* is only a possible explanation:

"I did not assert, that the ways I pitched upon were the true and genuine ones, by which Medicine does act, but only propounded them as ways by which it may act".<sup>102</sup>

As an alternative explanation Boyle suggests that in some cases Specific medicines may 'Mortify the over-Acid'.<sup>103</sup> This was, in fact, the general explanation put forward for medicines by earlier iatrochemists who believed disease to be a result of an excess of acid and the purpose of therapy to neutralize that excess.

Similar mechanical explanations were given to explain the action of poisons. Mead described Viper Venom as containing sharp, tenuous crystals which pierced

<sup>101</sup> Boyle, R., Experimental Naturall Philosophy, Oxford, 1664, part 2, p. 262.

<sup>102</sup> Boyle, R., Specifick Medicines, London, 1685, p. 135.

<sup>103</sup> ibid., p. 48.

and destroyed.<sup>104</sup> Aconite and other corrosive poisons consisted of 'Corrosive Vellicating Particles' which attack the stomach.<sup>105</sup> Lemery explained the vomiting and purging which followed the insertion of tobacco oil into a wound in the skin of a dog as being due to piercing sulphurous and volatile salts which had been carried to the stomach and pricked the constituent fibres.<sup>106</sup> This particulate theory was used to explain certain differences in action; for example, Mead explained the difference in action between the innocuous mercury metal and its poisonous salt corrosive sublimate (mercuric chloride) as being due to the saline particles which give sharp points and cutting edges to the metal.<sup>107</sup>

Although in the seventeenth century there was some knowledge of three important problems of pharmacology, viz absorption, dose-effect relationship and site of action, the foremost ideas of drug action were based on mechanical-chemical theories which postulated that action was due to the size, shape, motion and reaction of medicinal (and poison) particles. An outstanding consequence

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<sup>104</sup> Mead, R., Essays on Poisons, London, 1702, p. 9

<sup>105</sup> ibid., p. 126.

<sup>106</sup> Lemery, N., Cours de Chymie, Paris, 1677, p. 528.

<sup>107</sup> Mead, R., Essays on Poisons, London, 1702, pp. 107

of these theories was the belief that symptoms of disease might be reproduced, and effects of medicines might be examined in vitro, for example, the experiments carried out by Frederick Slare (1647-1727) and reported to the Royal Society in 1683.<sup>108</sup> Slare mixed the 'Volatile salt of Human blood' (the alkaline condensate obtained by destructive distillation of blood) with 'Spirit of Vinegar (the honey-like residue obtained by evaporating vinegar). The essential quantities of a tissue or fluid were believed to reside in the 'volatile salt',<sup>109</sup> and by mixing the volatile salt of blood with a concentrated acid substance, Slare believed he had reproduced in vitro a morbid condition of the blood. He interpreted the effervescence and cooling of the mixture as the explanation for the cold shivering fits of ague (malaria) and then proceeded to add to the mixture common remedies for that disease which included Opium, Quinine bark and Sulphur. He reported that only Opium brought about a reduction in the effervescence of the mixture. Yet

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<sup>108</sup> Birch, T., History . . . ., vol. 4, pp. 214, 217.

<sup>109</sup> Lemery, for example, wrote:

'La vertu des Animaux consiste  
principalement dans leur Sel volatile.'  
Cours de Chymie, Paris, 1677, p. 57.

another example of this reasoning applied to therapy occurs four years after Slare's report, when the Royal Society was told that coffee is safe for the nerves except for those who habitually drink wine, it having been observed that "coffee will put wine into a great ferment".<sup>110</sup>

The extreme iatro-chemical and iatro-mechanical view was put forward by Willis who wrote in the Preface to his Pharmaceutice Rationalis (London, 1679):

"But since almost the whole Business of this Pharmaceutrick Drame is acted behind the Curtain, therefore the various congressions of Particles, Fermentations, Impulses and other diversities of motions, which performed within ly hid from the senses, are to be searched out by a more deep Scruting of the Intellect."

In this way Willis hoped to render therapy into a "true science ..... not inferior to Mathematicks".

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Birch, T., History ....., vol. 4, p. 540.



At the end of the seventeenth century pharmacology was still dominated by the traditional and credulous materia medica. It had, however, been established that it was necessary to establish the modus operandi of drugs in order to render therapy exact in its application. It was believed that this might be accomplished by the simple application of chemical and physical laws with the result that the study of pharmacodynamics was neglected and experiment limited to simple toxicology.

## 2. GENERAL AND OFFICIAL PHARMACOLOGY IN THE EIGHTEENTH CENTURY

The credulity that had characterized therapeutics gave way slowly after the seventeenth century in the face of the rational modes of thought resulting from contemporary advances in science. The scientific approach led to considerable advances in anatomy and physiology; in the field of general pharmacology it gave rise to a pharmaceutical and chemical reformation of the Materia Medica, particularly in Britain and the Scandinavian countries. In the more complex field of pathology and therapeutics, however, where the difficulties facing the physician were considerable, the credulity of earlier times was replaced by speculation giving rise to the medical systems for which the eighteenth century is noted.

### (i) The Medical Systems

The humoral pathology continued to occupy the attention of the physicians and maintained the interest in the cathartic and emetic drugs. To this pathology and its variations there were added a number of systems based on a 'tension pathology' where disease was believed to be related to the tone of the nervous and

vascular systems. Friedrich Hoffman (1660-1742) put forward the theory that the body was composed of fibres having a characteristic tonus. Disease was a result of a deviation of the tonus from the normal and therapy consisted in the application of either sedatives or tonics to relax or stimulate the fibres according to the nature of the disease. William Cullen (1712-1790) of Edinburgh, extended the theory and related the tone of the solid parts of the body to nervous energy and the influence of external stimuli. Here again tonics featured prominently in the treatments derived from the theory and they included wine, quinine and camphor. Yet another variation was put forward by John Brown (1735-1788), a pupil of Cullen, who suggested that life was maintained by continuous stimuli which in turn maintained the excitability of the organs. Any change in this excitability resulted in disease. The therapeutics of the Brunonian system, as it came to be called, consisted of excessive doses of stimulants or sedatives. This therapeutic system achieved a considerable popularity and Brown had his followers among the physicians of Europe as well as of Britain. Among them was the Italian Giovanni Rasori of Parma (1766-1837) who later abandoned Brunonism and substituted a doctrine of

stimulation and counter-stimulation for Brown's condition of sthenia (too strong excitation) and asthenia (too weak excitation). Rasori's therapy was restricted to the use of one drug at a time but it followed Brown's in that massive doses were called for and he is said to have prescribed enormous doses of extract of aconite for the treatment of syphilis and no less than 75 grains of antimony tartrate to be given over four days for the treatment of pleurisy.<sup>111</sup> It is obvious that in some areas of clinical practice in the latter part of the eighteenth century there still existed a lack of appreciation of the relation between dose and effect and a disregard for the toxicity of the substances used - a factor of increasing danger as advances in pharmaceuticals and chemistry led to more concentrated vegetable extracts and purer chemicals.

The rise of these and similar systems during this period may be attributed to a desire for a unitary concept of disease. Investigation was in the hands of practicing physicians who were in need of a rapid solution to the problem before them and, instead of isolating single aspects for study, they took speculative jumps

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<sup>111</sup> Castiglioni, A., History of Medicine, New York, 1947, p. 593.

putting their faith in reason to the neglect of experiment.<sup>112</sup> The speculative habit of mind in medicine is evident throughout the century and in the last decade it gave rise to a new system of therapy when Samuel Christian Friedrich Hahneman (1755-1843) promulgated the principle of similia similibus curantur - diseases are cured by those substances which in the healthy induce symptoms of the disease.<sup>113</sup> At the same time, however, there were

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112 Castiglioni, A., History of Medicine, New York, 1947, pp. 578-582.

Shryock, R.H., Cah. Hist. Mond., 1957, 3, 882-3.

113 The doctrine similia similibus had its origin in 1790 when Hahneman was translating Cullen's Materia Medica (1789). Cullen spoke of the tonic effect of cinchona bark upon the stomach. Hahneman disagreed with this and began to take a course of cinchona to study its effects. After a time he developed symptoms which he interpreted as intermittent fever - the condition for which the bark is a cure. The doctrine was first expounded in a paper in Hufeland's Journal in 1796 entitled 'Essay on a New Principle for ascertaining the curative powers of drugs'. These observations gave rise to the system of homoeopathy. One of the features of this system was the belief that the effects of a drug increased as the dose decreased. Thus the doses used were minute and at least it can be said of homoeopathy that, if its therapy was in most cases useless, it

an increasing number of physicians who were influenced by research and discoveries of the exact sciences and who adopted and applied the experimental method to their own problems. They had little sympathy for the speculation and theories of their time and went to considerable trouble in their published works to describe their experiments and to show that every conclusion followed from actual observations. Such men agreed with the Abbate Felice Fontana (1730-1805), who, when considering the work of his contemporaries, ventured to suggest:

"A strict and accurate posterity will, without doubt, be astonished to find that in the eighteenth century there have been Philosophers, Naturalists and Physicians who, even in the most important matters have ventured to substitute conjecture for experience ..."<sup>114</sup>

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was, at the same time, harmless. This was of some importance in a time when polypharmacy and excessive doses featured in everyday medical practice.

<sup>114</sup> "La severe et juste Posterité sera étonnée sans doute de voir que dans le dixhuitième siècle il y ait en des Philosopes, des Naturalistes, des Physiciens, qui même dans les choses le plus importantes, ont osé substituer des conjectures à l'expérience ..." Fontana, F., Traité sur le Vénin de la Vipere, Florence, 1781, Vol. i, p. 71.

(ii) Changes in Official Materia Medica

In the field of official pharmacology during the eighteenth century the influence of science is evident in the gradual simplification of the materia medica. The change, however, was principally a pharmaceutical and chemical revision and the lack of a pharmacological basis resulted in changes that did not conform to any particular therapeutic pattern.

The need for a rejection of superstitious and traditional remedies was given recognition by the compilers of the fourth edition of the Pharmacopoeia Londinensis published in 1721. In the preface Sir Hans Sloane (1660-1753), then President of the Royal College of Physicians, refers to the rejection of medicines of superstitious origin but it is obvious from a study of the work itself that the ability to recognize such substances was very limited; for example, puppies, hedgehogs and wagtails were deleted, but human fat, human skull, mummy, Bezoar stone and the various excreta were retained.<sup>115</sup> The most significant feature of this work is the greater simplicity of some of the formulae and it has been described as a compromise

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<sup>115</sup> Pharmacopoeia Londinensis, 1721, fourth edition,  
pp. 38-39.

between the earlier polypharmacy and the simpler methods of prescription.<sup>116</sup> The compilers of the second edition of the Pharmacopoeia Edinburgensis (1722) followed the lead of their London colleagues and removed many drugs originally introduced by credulity and superstition, although they too failed to delete human products, scorpions, ants and viper fat.<sup>117</sup>

In 1738 the President (Henry Plumtre, died 1746) and the Censors of the London College began a new revision of their Pharmacopoeia.<sup>118</sup> When the work appeared in 1745, so different was it from its predecessors that the compilers claimed a reformation instead of a mere revision.<sup>119</sup> The work was a far-reaching simplification of the pharmacopoeia and was directed both at the out-of-date items of the materia medica and at the traditional formulae. The number of simples was reduced to 272 and of preparations to 378, the majority of which

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<sup>116</sup> Munk, W., Roll of the Royal College of Physicians, London, 1878, Vol. 3, p. 380.

<sup>117</sup> Pharmacopoeia Edinburgensis, 1722, Second edition, pp. 20-21.

<sup>118</sup> Munk, W., Roll . . . ., London, 1878, Vol. 3, p. 382.

<sup>119</sup> Pemberton, H., Dispensatory of the Royal College of Physicians, London, 1746, p. 1.



were composed of only one to four ingredients. As with the former edition it was largely a chemical and pharmaceutical revision based on the advances in chemical knowledge and on experiments in pharmaceutical compounding which had been entrusted largely to Henry Pemberton (1694-1771).<sup>120</sup> In therapeutics, however, it was not so successful for, although a great number of inert materials had been deleted, there were still retained such things as Bezoar stone, millipedes, viper and viper flesh. It is true, of course, that the inclusion of

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<sup>120</sup> Munk, W., Roll ..., London, 1878, Vol. 3, p. 383.

Henry Pemberton studied medicine in Paris, London and at Leyden under Boerhaave. After graduating M.D. in 1719 he returned to London, but delicate health prevented him from establishing a large practice. His interests turned to mathematics and chemistry and work in theoretical physics earned him the friendship of Newton who employed him to supervise the third edition of the Principia. In 1728 Pemberton was appointed Gresham Professor of Physic and ten years later he began the series of chemical and pharmaceutical experiments that were to lead to the reformed London Pharmacopoeia. He was a man of wide interests and abilities and Munk described him as 'an accomplished gentleman, and one of the best chemists of his age'.

these materials was justified at the time from the point of view that, when no other evidence is available, the compilers of a pharmacopoeia must be guided by current practice and there is ample evidence that these drugs were still highly regarded by practitioners.<sup>121</sup> Nevertheless, the compilers themselves were not fully convinced of the efficacy of all the medicines they included and they commented that the demands of current practice compelled them to leave the completion of their work to others:

"We have here endeavoured, as much as might be to retrench the excess: though in some things we have submitted to the prevalence of custom, and left them to the correction of posterity."

Preface, Pharmacopoeia Londinensis,  
1745.

(from the official translation  
by Henry Pemberton, London, 1746)

The 'prevalence of custom' of which the compilers complained forced them to include medicines which at the time were being severely criticized by distinguished

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<sup>121</sup> In 1745 Richard Mead, then President Elect of the London College, wrote at length and with enthusiasm on the medicinal virtues of viper flesh in the third edition of his A Mechanical Account of Poisons, London, 1745, p. 54.

sections of medical opinion. Of particular interest here is the example of the alexipharmics, Mithridate and Theriaca. In 1744 an anonymous author using the nom de plume 'M.S.' commented upon the inclusion of these preparations in a draft of the proposed pharmacopoeia describing them as irrational compositions that had been publicly condemned.<sup>122</sup> In the same year as the Pharmacopoeia was published, William Heberden (1710-1801), a member of the Pharmacopoeial Committee, described the alexipharmics as useless and even suggested that the traditional events leading to their formulation were false.<sup>123</sup> The first effects of these objections on the official materia medica occurred in 1756 when the Edinburgh College rejected the alexipharmics from the fifth edition of their pharmacopoeia. The London College followed suit in the next (sixth) edition of its pharmacopoeia published in 1788. In this respect Britain was in advance of other European countries where traditional and superstitious remedies were retained in official works for some time to come.<sup>124</sup>

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<sup>122</sup> H.S., Pharmacopoeia Reformata, London, 1744, p. 182.

<sup>123</sup> Heberden, W., ANTIÖHPIAKA. An Essay on Mithridatum and Theriaca, London, 1745.

The gradual rejection of inert and valueless medicaments from the London, Edinburgh and other official pharmacopoeias illustrates the gradual ascendancy of systematic and rational modes of thought over tradition and superstition in the materia medica. There was an exposure of the authority and prejudice existing in medicine. In 1753, Young wrote:

" .... they [writers on the materia medica] all agree that elks-hoof, for example, or the cranium humanum are good cephalics, yet you may reasonably suspect, that an hundred such

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- 124 The 6th edition of the Pharmacopoea Wirtenbergica 1798, still retained Electuarium Mithridatium Damocritas (p. 34), Electuarium Theriacae Andromanchi (p.35) and a number of animal drugs including Mumiae - Mumies d'Egypte - Egyptian Mummy  
Axungia Hominis - Menschenschmalz - Human Fat.  
 Later the Codex Medicamentarius sive Pharmacopoea Gallica, Paris, 1818, included one of the alexipharmics under the title Theriaca or Electuarium Opiatum Polypharmacum (p.317). The same work retained a number of animal drugs among them  
Lumbricus terrestris - Le Ver de Terre - Earth-worms.  
Testudo Lutaria - La Tortue bourbeuse - mud tortoise  
Vipera - La Vipere - Viper.

authorities are in reality but one; especially when we find, that most of these writers copy verbatim from others."<sup>125</sup>

He further condemned the prejudice which developed to such a degree that when "our prescriptions apparently do harm we are apt to describe to the malignity of the disease." <sup>126</sup>

It cannot be denied that the important changes in the pharmacopoeias at this time were principally influenced by a mode of thought derived from the success in physical and chemical sciences; William Cullen, for example, attributed the changes directly to chemistry.<sup>127</sup> Nevertheless, the need for a therapeutic and pharmacological approach did not go unrecognized even although systematic methods by which this might be achieved had yet to be firmly established. 'M.S.' advised the London College to see that "no new medicine how strongly recommended soever, receive the solemn sanction of the College

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<sup>125</sup> Young, G., A Treatise on Opium, London, 1753, p. 9.

<sup>126</sup> Ibid., p. 11.

<sup>127</sup> Cullen, W., Materia Medica, Edinburgh, 1789,  
Vol. 1, pp. 24, 31.

before its real merit be duely enquired into".<sup>128</sup>

Later on this same point he severely criticized the introduction of Pulvis Antilyssus, a supposed cure for rabies recommended by Sir Hans Sloane.<sup>129</sup> Although Pemberton's experiments on preparations for the 1746 pharmacopoeia resulted principally in a pharmaceutical simplification, it is true to say that they were conducted with therapeutic considerations in mind. His

<sup>128</sup> 'M.S!', Pharmacopoeia ..., London, 1744, p. x.

<sup>129</sup> Ibid., p. 152. Pulvis Antilyssus was composed of equal parts of the lichen Lichenis cinerei terrestris and Black pepper (Piperis nigri). In 1671 Sir Robert Moray exhibited the lichen before the Royal Society claiming that it had been shown by experiment to cure the bite of a mad dog. He stated that the Duke of York had caused it to be given to a kennel of dogs so bitten and all recovered with the exception of two who did not receive the medicine. In 1698 Hans Sloane claimed that a secret remedy in possession of the Dampier family contained the lichen and it was on his recommendation that the remedy was included in the London Pharmacopoeia. For a time the preparation bore his name Pulvis antilyssus sloanii.

see: Birch, T., History ..., London, 1756,  
Vol. 2, p. 492.

Phil. Trans., 1698, 20, 49.

work was an attempt to give full effect to the active ingredients, and in pursuance of this aim Pemberton and the revision committee endeavoured to prevent the mixing of medicines having opposite effects as well as to reduce excessive dilution of the active principles.<sup>130</sup> The reference to pharmacological experiments, however, is negligible in the deliberations of the London revision committee of 1745. The only reference given is the exclusion of Black Cherry Water, a distillate of cherry-stones.<sup>131</sup> On examination this cordial was discovered to be as toxic as Cherry Laurel Water, a similar liquor which had been extensively studied by means of experiment on animals. (See infra for the work of Madden (1728), Mortimer (1731) and Browne Langrish (1734)).

Although, as we have seen, clinical experience alone was inadequate to form a scientific basis for the evaluation of drugs, the greater precision of approach in clinical practice which developed during this century had an effect upon the materia medica and the official pharmacopoeias. Herman Boerhaave (1668-1738) whose teaching at Leyden influenced physicians throughout Europe, was an iatro-mechanist in theory, but he

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<sup>130</sup> Pemberton, H., Dispensatory, London, 1746, p. 4.

<sup>131</sup> Ibid., p. 76.

taught care, precision and observation in practice. He taught the need for observation and experience in the determination of medicinal properties and believed that a knowledge of medicines was obtained either by careful observation and comparison between one case and another or by careful reasoning from both.<sup>132</sup>

Boerhaave's distinguished pupil Albrecht von Haller (1708-1777) outlined a practical approach to this problem in his Preface to the Pharmacopoea Helvetica (Basle, 1771):

"In the first place the remedy is to be tried on the healthy, without any foreign substance mixed with it; having been examined as to its odour and taste, a small dose is to be taken, and the attention directed to all effects which thereupon occur: such as upon the pulse, the temperature, the respiration, the excretions. Having thereby adduced their obvious phenomena in health, you may pass on to experiment upon the sick body." <sup>133</sup>

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<sup>132</sup> Boerhaave, H., Aphorismi de Cognoscendis et curandis morbis, Francofurti, 1710, p. 2.

<sup>133</sup> Nempe primum in corpore sano medela tentanda est, sine peregrina ulla miscela; odoreque et sapore ejus exploratis, exigua illius dosis ingerenda et ad omnes quae inde contingunt affectiones, qui



A practical application of these principles was carried out with a number of vegetable drugs by Stoerk (vide infra) and the vegetable drugs recommended by him were later introduced into the 6th edition of the Edinburgh Pharmacopoeia, the compilers of which were resolved to accept only such new drugs as were supported by the experience of the College itself or by some other responsible recommendation.<sup>134</sup>

(iii) Pharmacological Classifications of Medicines

New attempts were made in the eighteenth century to classify medicines according to their observed (or supposed) physiological and therapeutic effects. Broad classifications had been used since the seventeenth century, for example, by Joseph-Pitton de Tournefort (1656-1708), who divided drugs primarily into those that evacuate and those that alter the humours.<sup>135</sup> Boerhaave

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pulsus, quis calor, quae respiratio, quatenus excretiones, attendendum. Inde adductum phenomenorum in sano obviorum, transeas ad experimenta in corpore aegroto.

<sup>134</sup> Pharmacopoeia Edinburgensis, 1774, Sixth edition, p. xiv.; Medical and Philosophical Commentaries, 1774, 2, 415; see also footnote <sup>157</sup>.

divided medicines into three classes, one, those acting on the solids of the body (included stimulating, relaxing and corrosive drugs); two, those acting on the liquids (includes attenuating and demulcent substances); and three, the largest group, those which act on the solids and liquids (include sialogogues, cholagogues, emetics, diuretics and aperients).<sup>136</sup> Classification was carried to an extreme by Linnaeus who arranged pharmacological and physiological effects into classes, orders and sub-orders (see Plate IV). The drugs themselves were listed in sub-orders in the Index virium<sup>137</sup> where they were arranged simply according to reported action. Although this classification served as a guide to effects, it was nevertheless unsatisfactory, and this may clearly be seen in the case of those drugs in which the effect varied with dose, or which have more than one effect.

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<sup>135</sup> Tournefort, J. Pitton de..., Materia Medica, London, 1708, Preface. Note: Tournefort's lectures on the materia medica were first published in English. A French edition did not appear until 1717. See bibliography.

<sup>136</sup> Boerhaave, H., Tractatus de Viribus Medicamentorum, Paris, 1723, p. 68, et seq.

<sup>137</sup> Linnaeus, C., Materia Medica, lib. I., De Plantis, Holmiae, 1740, p. 242.

# VIRES.

Qualitates I. Principia Vegetabilium vim & actionem suam exerunt in corporis humani vel *Liquida*, vel *Solida*, vel ex Solidis Liquidisque composita *Vitæ*.

*LIQUIDA* vel evacuando vel alterando.  
*SOLIDA* vel in fibras Nerveas vel Musculares agendo.  
*SOLIDO LIQUIDA* vel Internis vel Externis medendo.

<i>Classes.</i>		<i>Ordines.</i>
Liquida	EVACUATORIA, e corpore exterminantia.	{ Purgantia. Borborygmica. Pellentia. Pituitosa.
	ALTERANTIA. massam sanguineam e- mendantia.	{ Discrasiva. Diathetica.
Solida	NERVINA. in nervos agentia.	{ Orgastica. Convulsiva. Excitantia. Stupescientia. Phantastica.
	MUSCULARIA. in musculosas fibras a- gentia.	{ Relaxantia. Corroborantia. Corrodentia.
Solido-Li- quida.	VISCERALIA. viscera petentia.	{ Spirituosa. Biliofa. Mucagnosa. Venerea.
	TOPICA. externe applicabilia.	{ Consolidantia. Dissolventia. Astringentia.

## *Classis I.*

### EVACUANTIA I. PURGANTIA.

evacuantia liquida intra tubum intestinales composita.

1. EMETICA. *Vomitoria* 97.  
evacuant ventriculum per Oesophagum.
2. DRASTICA. 31.  
evacuant intestina & ventriculum per anum violentissime.
3. CATHARTICA. *Purgantia* 71.  
evacuant intestina per anum moderate.
4. ECCOPROTICA. 32. *Laxativa, Laxantia.*  
evacuant intestina per anum debillissime.
5. FLATULENTIA. 46.  
Flatibus abdomen distendunt.
6. RUPTATORIA 77.  
Flatibus per Oesophagum exallunt.

### II. BORBORYGMICA.

evacuantia status intra tubum intestinales composita.

Plate IV. Linnean classification of medicines.

Opium, for example, is listed without comment under both Hypnotica (order Stupefacientia) and Exhilarantia (order Excitantia)! In the main body of Linnaeus' work the medicines are arranged and discussed according to their source, - a common method of presentation at that time but unsatisfactory since drugs of widely different sources often have similar therapeutic and pharmacological properties. An alternative method of presentation of the materia medica was adopted by Cullen:

" .... as the study of the materia medica is truly the study of the medicinal virtues, so the plan that arranges the several substances according to their agreeing in some general virtues, will be the best adapted to acquiring the knowledge of these and will most readily inform the practitioner that different means he can employ for his general purpose." 138

His plan, therefore, was to group together substances having similar therapeutic and pharmacological effects and to discuss them under the headings tonics, astrin-  
gents, sedatives and so on. Similar methods of

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138 Cullen, W., Materia Medica, Edinburgh, 1789,  
Vol. i, p. 158.

presentation had already been used by Chomel,<sup>139</sup>  
Lieutard<sup>140</sup> and Spielmann.<sup>141</sup>

(iv) Pharmacotherapeutic Studies of Hemlock, Digitalis  
and other Vegetable Poisons

The classifications were based on existing knowledge concerning the effects of drugs and they served only to guide the practitioner in his choice of medication. Of greater importance to the future of the subject were the growing number of investigations concerning the use of drugs for the treatment of specific diseases, for example, the use of Ipecachuanna for dysentery, the Mercurials for venereal disease and Cinchona bark for fevers.<sup>142</sup> This work was largely the result of observation and investigation in the course of clinical practice;

<sup>139</sup> Chomel, P.J.B., Abrégé de L'Histoire des Plantes  
Usuelles, Paris, 1712.

<sup>140</sup> Lieutard, J., Precis de la matière médicale, Paris,  
1766.

<sup>141</sup> Spielmann, J.R., Institutiones Materiae Medicae,  
Strasbourg, 1774.

<sup>142</sup> see Waring, E.J., Bibliotheca Therapeutica, London,  
1878-9, Vol. i, p. 339, et seq., Vol. ii,  
p. 468 et seq., p. 526 et seq.

and of the contributions from this source, those of Stoerk and of Withering are of particular importance and interest to the history of pharmacology.

Anton Freiher von Stoerk (1731-1803) studied in Vienna under Gerard van Swieten (1700-1772) a student of Boerhaave, who, in 1745, was entrusted by Maria Theresa with the task of reforming the Faculty of Medicine in the capital. A clinic was established under the directorship of another student of Boerhaave, Anton de Haen (1704-1776), and there it was possible to study disease and treatments under reasonably controlled conditions. Stoerk's early studies therefore developed in an atmosphere of precise clinical teaching derived from Boerhaave and extended by two of his eminent pupils. In 1757 Stoerk was awarded his doctorate and three years later he was appointed physician in ordinary to the Empress. He later succeeded van Swieten as director of the medical faculty and in 1770 he was created a baron; by this time his position in Austria and his influence beyond its frontiers were considerable.

The principal pharmacological studies carried out by Stoerk were concerned with the poisonous plants hemlock (Conium maculatum, L), stramonium (Datura stramonium, L), henbane (Hyoscyamus niger, L.), aconite



(Aconitum napellus L.) and colchicum (Colchicum autumnale L.). He believed these toxic drugs, if properly prepared, extracted and given in small doses, would prove beneficial for certain diseases. His first and principal work was with hemlock and his results were published in Vienna in 1760 under the title: Libellus, quo demonstratur: Cicutam non solum usu interno tutissime exhiberi, sed et esse simul remedium valde utile in multis morbis, qui hucusque curatu impossibiles dicebantur. The book was immediately translated in English and Dutch and shortly appeared in the French and Italian.<sup>143</sup> It aroused considerable interest, but such was the opposition to it, particularly among his own colleagues, that the author was obliged, in 1761, to publish further results in answer to the criticisms.<sup>144</sup> The results of the studies of stramonium, henbane and aconite were published in 1762<sup>145</sup> and those of colchicum

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<sup>143</sup> English - London, 1760; Dutch - Rotterdam, 1760; French - Vienna and Paris, 1761; Italian - Turin, 1762.

<sup>144</sup> Libellus Secundus, quo confirmatur: Cicutam non solum usu interno tutissime exhiberi, .... etc., Vindobonae, 1761. and Supplementum necessarium de Cicuta, ubi simul jungitur cicutae imago aere excusa, Vindobonae, 1761.

<sup>145</sup> Libellus, quo demonstratur: Stramonium, Hyosciamum,

followed in 1763.<sup>146</sup> Some years later Stoerk reported similar studies with clematis (Clematis alba L.) Bastard Dittany (Dictamnus albus)<sup>147</sup> and Meadow ~~an~~emone (Anemone Pulsatilla)<sup>148</sup>.

In these works Stoerk recorded a number of case histories to demonstrate the medicinal virtues of these plants together with the preliminary experiments he carried out before the substances were administered in treatments. The plants he was studying were not unknown to medicine but, so that his experiments concerning dose, toxicity and mode of administration might be objective, he deliberately disregarded the literature:

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Aconitum non solum tuto posse exhiberi use interno hominibus, verum et ea esse remedia in multis morbis maxime salutifera, Vindobonae, 1762.

146 Libellus, quo demonstratur: Colchici Autumnalis Radicem non solum tuto posse exhiberi hominibus, sed et ejus usu interno curari quandoque morbos difficillimos, qui aliis remediis non cedunt, Vindobonae, 1763.

147 Libellus, quo demonstratur: Herbam, Veteribus Dictam Flammulam Jovis, Posse tuto et magna cum utilitate exhiberi aegrotantibus, Viennae, 1769.

148 Libellus de usu medico Pulsatillae nigrantis,  
Vindobonae, 1771.



"In order to carry out experiments without prejudice, I disregarded all I had learnt from writers of the *materia medica*, remembering only that it [*Aconite*] was a suspected plant." 149

Stoerk began by describing the plant and in the case of hemlock he goes so far as to specify the time of collection.<sup>150</sup> He then described his method of preparation for administration, for example, the juice is expressed from the leaves and stem of hemlock and evaporated to the consistency of an extract. Similar preparations are made with stramonium, henbane and aconite. Colchicum was administered in the form of an 'oxymel' - a decoction of the corm in a mixture of honey and vinegar. Using these standard preparations Stoerk went on to carry out simple tests upon himself and on dogs in order to determine the toxicity, the effects of the drug and a suitable dose. This was a practical example of the method later described by Haller in the Pharmacopoea

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149 Experimenta, ut rite fierent, & sine praejudicio, delevi omnem in me ideam, quam habui ex auctoribus materiae medicae, id tantum retinui: plantam esse suspectam. Libellus ... Stramonium, Vindobonae, 1762, p. 33.

150 Libellus Secundus, ... Cicutam, Vindobonae, 1761, p. 2.

Helvetica (see p.84 ). . . With hemlock, twenty grains of the extract was given to a dog without effect, after which Stoerk himself took first one grain of the material ~~and~~ then two, without noting any symptom of poisoning. The results of these trials directed him to prepare two-grain pills for administration to the patients beginning with a one-pill dose which was gradually increased.<sup>151</sup>

In the course of these preliminary experiments Stoerk observed the depressant and mydriatic effects of hyoscyamus,<sup>152</sup> the sialogogic and diaphoretic action of Aconite<sup>153</sup> and the irritant properties of colchicum describing symptoms of both gastro-intestinal and renal irritation (colic, tenesmus and bloody stool; initial diuresis followed by anuria and haematuria).<sup>154</sup>

In his therapy Stoerk does not always display the logical approach evident in his studies of toxicity and dosage, following, as he does, speculative ideas based on his observations and on reports in the literature.

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<sup>151</sup> Libellus ... Cicutam, Vindobonae, 1760, pp. 7, 8, 12.

<sup>152</sup> Libellus ... Stramonium, Vindobonae, 1762, p. 14.

<sup>153</sup> Ibid., pp. 33-35

<sup>154</sup> Libellus ... Colchici Autumnalis, Vindobonae, 1763, pp. 11, 17 et seq.

Hemlock extract was administered as a remedy for a number of diseases including cancer, scirrhus, cataract, skin diseases, ulcers and rickets. A number of successful treatments are recorded mostly for cancers and scirrhus. He suggested that stramonium, a poison reported in the literature to affect the mind and cause convulsions, might be used to cure madness:

" ... If Thorn-apple, by disordering the mind, causes madness in sound persons; may we not try, whether by disturbing and changing the ideas and common sensory it might not bring the insane, and the persons bereft of their reason, to sanity or soundness of mind; and by a contrary motion remove convulsions in the convulsed?" 155

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155 Si Stramonium turbando mentem adsert insaniam sanis, an non licet experiri: num insanientibus & mente captis turbando, mutantque ideas, & sensorium commune adserret mentem sanam, & convulsis contrario motu convulsiones? Libellus ... Stramonium, Vindobonae, 1762, p. 4.

The translation given in the text is taken from the English edition : An Essay on the Internal Use of Thorn-apple, Henbane and Monkshood, London, 1763, p.4.

Professor Schild of University College, London, in a private communication to the author, has suggested that Stoerk's reasoning would be considered sound

He reported its use in five cases but they do little to support his reasoning.

The use to which the other drugs were put, however, was determined by reference to the observations made in the preliminary experiments. The 'anodyne' henbane was given for the treatment of convulsions, epilepsy and other 'nervous' disorders; the mildly diaphoretic aconite for ague, gout, venereal disease and other conditions where it was necessary to expel 'peccant' matter. Calchicum, because of its apparent diuretic properties, was employed for the treatment of dropsy and ascites.

The treatments were symptomatic and success was achieved when the symptoms disappeared. To explain the action of the drug in such cases Stoerk simply introduces the theory of the expulsion of morbid matter. Thus gout, scirrhus and cancer, conditions believed to be caused by an obstruction or coagulation of 'peccant' matter, were all said to have been cured by hemlock which must, therefore, possess a great resolving quality enabling it to reach parts

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today and has found an application in the use of such substances as d-lysergic acid diethylamide (LSD) in psychotherapy.

156 Supplementum ... Cicuta, Vindobonae, 1761, p. 35.

other remedies could not touch, and to remove the obstructions and cancers! <sup>156</sup>

Stoerk's researches met with a mixed reception: on the one hand they were considered sufficient recommendation of the introduction of these drugs into certain official pharmacopoeias,<sup>157</sup> while on the other they met hostility and disbelief. His principal opponents appear to have been among his own colleagues, particularly

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<sup>157</sup> The Edinburgh Pharmacopoeia of 1774, (the sixth edition and the first to be published after the Stoerk's work) added Stramonium, Aconite, Pulsatilla and Colchicum. (Hemlock and Hyoscyamus were already included in the materia medica.)

The first edition of the London Pharmacopoeia after Stoerk's researches was not published until 1788 (6th edition). The work included Hemlock, Aconite and Colchicum. An oblique reference to Stoerk's work appears in the Preface to this edition when it says that Medicine is no longer adverse to poisons but now makes use of them as allies and auxillaries.

"A few of these (which we have ourselves tried) we have enrolled in our list, ready to adopt others if faithful experiments made in the cure of diseases, shall demonstrate their efficiency."

Pharmacopoeia Londinensis, 1788,  
Heald's translation, p.ix.

his senior, de Haen.<sup>158</sup> Cullen, although he dismisses de Haen's objections as those of a 'declared enemy', goes so far as to suggest that Stoerk had been led astray by "a partiality of his own discovery" and "from much false information given in complaisance and adulation to the rank he holds".<sup>159</sup> In the early nineteenth century it was still being said that the value of hemlock was only supported by the reports of Stoerk and his friends,<sup>160</sup> although, Pereira was less inclined to doubt the integrity of the Viennese physicians than the nature of the diseases they were supposed to have cured:

"I am not prepared to offer any opinion, as to whether the diseases to which the term scirrhus and cancer are strictly applicable, have ever been cured by hemlock. One fact is undoubted that diseases supposed to have been scirrhus and cancerous, have been greatly alleviated, and, in some cases, apparently cured by this remedy." <sup>161</sup>

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<sup>158</sup> Supplementum ... Cicutae, Vindobonae, 1761, preface.

<sup>159</sup> Cullen, W., Materia Medica, Edinburgh, 1789, vol. ii,

<sup>160</sup> Woodville & Hooker, Medical Botany, London, <sup>p. 263</sup> 3rd ed., 1832, Vol. i, p. 107.

<sup>161</sup> Pereira, J., Materia Medica, London, 3rd ed. 1850, Vol. ii, p. 1730.

In view of the many criticisms it is important to draw attention to the fact that Stoerk made no claim that hemlock was an inevitable or even a complete cure for these diseases. He admitted that it had failed in certain cases of cataract and cancer even when, from experience, its use was clearly indicated.<sup>162</sup> It was this variation in results that prompted him to recommend hemlock to his fellow physicians that they might continue to make trials, the results of which might lead to the reason why in some cases it is of service and in others of no apparent use at all.<sup>163</sup> What is significant about this work is that the method used had made these trials possible. The tests for toxicity had shown that an extract of hemlock could be given in small doses with safety, thus removing the fear and prejudice surrounding this plant of ill-fame. Furthermore by describing the plant, its collection, preparation and dose, he had established a procedure which any who wished to test his claims might follow. Unfortunately, although it was possible to follow his method closely

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<sup>162</sup> Libellus Secundus ... Cicutam, Vindobonae, 1761,  
pp. 190, 287.  
Supplementum ... Cicuta, Vindobonae, 1761, p. 51.

<sup>163</sup> Ibid., p. 56.

(within certain limits),<sup>164</sup> it was unlikely that his problem could be solved in the manner he suggested since there was no clear definition of the exact nature of the diseases he had treated. This difficulty, as we shall see, was not so obvious when it came to confirming Withering's work with foxglove.

William Withering (1741-1799) studied medicine at Edinburgh and among his teachers were Alexander Monro, primus, one-time student of Boerhaave, his son Alexander Monro, secundus, and William Cullen. After graduation in 1766, he returned to his home in the Midlands, where he developed a large and successful practice, at the same time taking an active interest in botany, chemistry and mineralogy, to all of which he made important contributions.

Withering, like Stoerk, distrusted the earlier literature on the *materia medica*, believing it to be safer

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<sup>164</sup> The limits relate to the strength of the extract. Coniine, the active constituent is both thermolabile and photosensitive. In the Supplementum.. Cicuta, p. 9, Stoerk described the extract as having an odour of mice. This characteristic smell indicates the presence of the alkaloid, but the method of preparation would suggest variations in concentration from extract to extract.



to begin anew:

" .... a little advantage can be reaped from the experience of former times: we shall sooner attain the end proposed, if we take up the subject as altogether new, and rejecting the fables of the ancient Herbalist, build only upon the basis of accurate and well-conceived experiments." 165

He was not unaware of the dangers of creating a modern 'fable' concerning the action of a new drug and knew that only careful, scientific reporting of observations would avoid the danger:

"It would have been an easy task to have given selected cases, whose successful treatment would have spoken strongly in favour of the medicine, and perhaps been flattering to my own reputation. But Truth and Science would condemn the procedure. I have therefore mentioned every case in which I have prescribed the Foxglove, proper or improper, successful or otherwise." 166

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165 Withering W., A Botanical Arrangement of British Plants, Birmingham, 1776, Vol. i, p. xv.

166 Withering W., An Account of the Foxglove and Some of its Medicinal Uses; Birmingham, 1785, p. vi.

The Foxglove (*Digitalis purpurea*) was well-known to medicine in Withering's time. Dr. Stokes of Stourbridge,<sup>167</sup> a friend of Withering, traced its history and uses since it was described by Leonhard Fuchs in his De historia stirpium (first published in 1542). He refers to statements by Dodonaeus, Ray, Gerarde, Parkinson and Baylies, noting that the drug had been recommended for a variety of diseases including epilepsy, scrophulous ulcers, wounds and caries. Although used occasionally as a medicine, it was largely neglected because of its known toxic properties. It had been demonstrated in 1743<sup>168</sup> that the leaves were poisonous to birds, but of more significance was its description as a dangerous medicine by Boerhaave and Haller.<sup>169</sup> The possible value of foxglove to medicine was recognized by Charles Alston, (1683-1760), Cullen's predecessor in the chair of Materia Medica at Edinburgh, who described it as one of the indigenous plants "which though now

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<sup>167</sup> Withering, W., An Account of the Foxglove and Some of its Medicinal Uses, Birmingham, 1785, pp. xiv-xx.

<sup>168</sup> Salerne, F., Hist. Acad. R. Sci., 1748, (pub. 1752) p. 84.

<sup>169</sup> Haller, A., Stirpium Helvetiae, Gottingae, 1742, Tom. II, p. 617; Cowan, D.L., Med. Hist., 1957, i, 126.

disregarded, are medicines of great virtue, and scarcely inferior to any that the Indies afford".<sup>170</sup> The medicines from the Indies included the well-known and well-recommended Ipecachuanha and Sarsaparilla, which as Withering pointed out are but the medicines of the common people of the countries in which they are found.<sup>171</sup> He had good reason to pay homage to folk-medicine since it was the source of his own knowledge of the therapeutic properties of digitalis.

In 1775 Withering's attention was drawn to a family recipe for the treatment of dropsy which had for many years been the secret of a woman living in Shropshire. He reports that the recipe was composed of twenty or more different herbs and of these he chose foxglove as the active constituent. One of his biographers has stated that how he knew foxglove to be the active constituent must remain unexplained.<sup>172</sup> Withering himself simply says "it was not very difficult for one conversant with

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<sup>170</sup> Alston, C., Index Medicamentorum Simplicium,  
Edinburgh, 1752, p. iv.

<sup>171</sup> Withering, W., Botanical Arrangement, Birmingham,  
1776, Vol. 1, p. xv.

<sup>172</sup> Peck, T.W., & Wilkinson, K.D., William Withering  
of Birmingham, Bristol, 1950, p. 71

these subjects to perceive that the active herb could be no other than the Foxglove".<sup>173</sup> This statement rules out any suggestion that his choice of foxglove was a good guess. Withering had been told two things about the recipe: it was reputed to cure dropsy and, in certain cases, it induced violent vomiting and purging. The latter effects had been imputed to digitalis by both Ray and Haller, and it is not unreasonable to assume, that Withering, recognizing some of the effects of the recipe to be directly attributable to foxglove, naturally chose it as the obvious drug for further investigation.

Withering investigated the action of the drug in the course of his extensive clinical practice. He did not believe that drugs could be investigated for their effects by noting their sensory characters or by chemical analysis. He was certainly of the opinion that effects could be deduced by analogy from the effects of similar species, but this did not assist him in the present instance. The method of investigation by experiments with animals he rejected, because "it has

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<sup>173</sup> Withering, W., An Account of the Foxglove,  
Birmingham, 1785, p. 2.

not yet been much attended to".<sup>174</sup> He prepared standard preparations from the leaves gathered from the flowering plant: the leaves were either dried and finely powdered for administration or made into an infusion. Carefully determined doses were administered to selected patients. Withering's opportunities for testing the drug were considerable, for at this time he was attending the sick poor in the neighbourhood and between two to three thousand patients waited upon him annually for advice. Among them there were a number of cases of dropsy which responded well to the treatment, being cured by what Withering believed to be the diuretic effect of the foxglove - an effect unrecorded before his work. Although he attributed its effects to action on the kidneys, its effects upon the heart had not passed unobserved. His earliest rule for determining the correct dose for the patient was to give the drug until the urine flowed or until sickness or purging intervened. In some cases, however, none of these effects took place, and the dose was increased with the result that the pulse was considerably retarded.<sup>175</sup> This observation led Withering to the

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<sup>174</sup> Withering, W., An Account of the Foxglove,  
Birmingham, 1785, p. 1.

<sup>175</sup> Ibid., p. 186.

conclusion that digitalis "has a power over the motion of the heart to a degree yet unobserved in any other medicine".<sup>176</sup> He failed to associate this action on the heart with the diuretic action, but, in spite of this, his observations enabled him to describe with some accuracy those symptoms of heart disease which most readily respond to the action of digitalis:

" ..... if the pulse be feeble or intermitting, the countenance pale, the lips livid, the skin cold, the swollen belly soft and fluctuating, or the anasarcaous limbs readily pitting under pressure of the finger, we may expect the diuretic effects to follow in a kindly manner".<sup>177</sup>

In this way Withering described for his colleagues the symptoms of the condition for which foxglove was the cure (cf. Stoerk) and he was understandably annoyed when they doubted its efficacy after administering it without due regard to his instructions concerning its use. John Coakley Lettsom (1744-1815), a distinguished London physician, for example, failed to achieve results because he used the drug to treat ascites which had resulted from

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<sup>176</sup> Withering, W., An Account of the Foxglove,  
Birmingham, 1785, p. 192.

<sup>177</sup> Ibid., p. 189.

178, 179

cirrhosis of the liver consequent on alcoholic excess.

Stoerk and Withering conducted their researches in the course of their clinical practice, and their work is outstanding among the empirical clinical studies of that period. The monograph on a 'favourite medicine' was familiar to eighteenth-century medicine, but rarely had medicines been so carefully standardized in preparation and dose as hemlock and foxglove or the work so carefully reported that others might confidently seek confirmation of the published case-histories. Even so, this work contributed only indirectly towards a greater

178 Lettsom, J.C., Memoirs of the Medical Society of London, 1789, 2, 145; see also Withering's letter to Lettsom quoted by Peck and Wilkinson op.cit. (172), p. 82.

179 It should be noted that the digitalis was abused both before and after Withering's publication of his results. His earliest experiences with the drug were communicated to the Medical Society of Edinburgh by Stokes in 1779 and the drug was included in the Edinburgh Pharmacopoeia of 1783. One of the purposes of the publication of the research in 1785 was to correct the misuse of the drug which was in danger of being discredited for a second time in its history. Withering, W., Account of the Foxglove, p. 7. Roddis, L.H., Ann. Med. Hist., 1936, 8, 107. Cowen, D.L., Med. Hist., 1957, i, 127.

knowledge of the mode of action of these drugs. The work was pharmacotherapeutic and the results were always discussed in relation to the disease cured or the symptoms treated, and the few pharmacodynamic observations were incidental to the main purpose. The work of Withering, in spite of its success, serves to illustrate the difficulties associated with the study of the action of drugs during the course of medical practice. The subject is a sick human being and a new drug can be tried only when all others have failed, so that Withering, in his early work, could try the remedy only in the most hopeless cases, those "lost to the common run of practice". Fortunately for the reputation of the drug, these patients were not beyond its powerful aid, but one might imagine other drugs, used in similar situations, being condemned or thought worthless because the patient died when he might have lived, had the remedy been applied earlier. An additional and confusing factor is that in the clinical situation, a physician rarely employed a single drug and, as one writer points out, in cases where hemlock has been reported as of value for scirrhus, mercury was often administered at the same time.<sup>180</sup>

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<sup>180</sup> Duncan, A., The Edinburgh New Dispensatory,  
Edinburgh, 1810, 5th Ed., p.248.



The practising physician was too involved with the patient, the disease and the dictates of his profession concerning the welfare of the sick, to be absolutely objective on the subject of the mode of action of drugs. Such objectivity could be achieved only in laboratories with experimental animals after the manner of Wepfer and Harder. Of the number who worked in this manner nearly all were physicians, and often their ultimate object was therapeutic or toxicological information; nevertheless it is their work rather than that of Stoerk and Withering that is in direct line with the research of modern pharmacology.

### 3. EXPERIMENTS ON ANIMALS WITH DRUGS AND POISONS IN THE EIGHTEENTH CENTURY

#### (i) Experiments by Stephen Hales with some common 'liquors'

The Reverend Stephen Hales (1677-1761), of Teddington in Middlesex, was one of the ablest experimenters of the early eighteenth century. A Fellow of the Royal Society, he made a number of important contributions to science and is best remembered for his discoveries in plant and animal physiology. His work may be regarded as the most important contribution to the physiology of blood circulation after Harvey and his outstanding achievement was an estimate of the blood pressure by measurement of the height of a column of blood in a tube inserted into the femoral artery of a horse.<sup>181</sup> In the course of this work he developed a method of studying the circulation in the abdominal arteries and of measuring the resistance set up by the capillaries.<sup>182</sup> He was later to use the same

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<sup>181</sup> Hales, S., Statical Essays, London, 1733, Vol. 2. This volume is sub-titled: Haemastatics: or, An Account of some Hydraulic and Hydrostatical Experiments made on the Blood and Blood Vessels of Animals.

<sup>182</sup> Ibid., p. 48.

technique to study the effects of certain solutions or 'liquors' on the blood vessels.

The technique used was as follows:

Hales cut the jugular vein of a young spaniel dog, weighing  $2\frac{1}{2}$  pounds, and allowed it to bleed to death. He then opened the thorax and abdomen and with the aid of a brass connection, inserted a glass tube,  $4\frac{1}{2}$  feet high, into the descending aorta just below the heart. This tube, when filled with fluid, exerted a force approximately equal to the force with which the blood is impelled by the heart.<sup>183</sup> After the insertion of the tube the gut was cut along its entire length on the side opposite to the insertion of the mesenteric arteries and veins. The parts were covered with warm water and then with a cloth soaked in water at the same temperature. Warm water was then poured through a funnel at the top of the tube and allowed to flow through the tube and blood vessels until it remained level with a predetermined mark at the bottom of the funnel. The subject was now prepared and ready for

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<sup>183</sup> Ibid., pp. 48, 114. In his first experiment to measure the blood pressure of the horse, Hales recorded the bore of the brass connection tube to be 0.057 sq. inches (0.3 inch diameter). The glass tube was said to be of a similar bore.

the determination of the effects of various liquors on the blood vessels through which they were passed.

Eighteen cubic inches (10 fluid ounces) of warm water were poured into the funnel and the time was taken (by means of a pendulum beating seconds) for the same volume to emerge from the mesenteric arteries, i.e. the time for the level of the water to fall to the original mark. The process was repeated seven times with water and then repeated five times using the same volume of "common Brandy or unrectify'd Spirit of Malt". The investigation was completed by passing a final volume of warm water. The results of this experiment are summarized in Table I. By comparing the time for the spirit to pass with the time taken by the control (warm water), Hales concluded that brandy contracts the fine capillaries of the intestines.<sup>184</sup> The choice of brandy for this first investigation was prompted by Hales' concern for the detrimental effects of the consumption of large quantities of spirits and his recognition of the need for reform in an intemperate age.

Using the same technique he went on to examine

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<sup>184</sup> Ibid., p. 128.

the effects of some medicinal liquors. He prepared a decoction of Peruvian bark (cinchona) by boiling a pound of the bark with three gallons of water and concentrating by evaporation to two gallons. Volumes of this solution were passed through the tube using warm water as a control.<sup>185</sup> The results of the experiment are summarized in Table II. The slowing up of the rate of passage of the decoction was interpreted as being due to the contracting or 'Stiptic Quality' of the solution.<sup>186</sup>

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<sup>185</sup> Statistical Essays, London, 1733, Vol. 2, p. 131.

<sup>186</sup> In view of this conclusion it is worth noting that Styptic medicines were a constant source of interest at this time owing to recognition of the value of an efficient haemostatic to military medicine. Considerable interest was shown, for example, in an 'astringent liquor' reported to the Royal Society in 1673 (Phil.Trans., 1673, 8, 6039). Experiments with the remedy (which was secret) were carried out by the Fellows on the cut arteries and amputation stumps of dogs. Later trials were made on calves before the King at Whitehall (Phil.Trans., 1673, 8, 6052, 6054). After reports on its success in cases of amputations in humans, the King ordered a quantity of the material to be prepared and sent to the Fleet. A letter from a surgeon in the Fleet later reports that the 'Royal Styptic Liquor' was used on the wounded after an engagement with the Dutch (Phil.Trans., 1673, 8,

Probably this supposed styptic property determined his choice of the next liquid for test; this was the astringent decoction of oak bark<sup>187</sup> (see Table III). In another experiment Hales used two solutions, a decoction of Chamomile Flowers and a decoction of Cinnamon bark.<sup>188</sup> This proved to be a confused experiment in which he forgot the initial control process of passing warm water and deviated from the normal practice by passing very hot solutions. The results for what they were worth indicated that the solutions possessed styptic or astringent

6115). A number of likely substances were investigated for styptic properties and in 1752 it was reported that a fungus growing on oak trees was effective, even closing large arteries (Phil.Trans., 1752, 47, 560). Unfortunately, few of the styptics lived up to the reputation their discoverers claimed for them. Many silently disappear from the literature; others were openly contested. Thus in 1694 William Cowper, a surgeon reported that a substance known as 'Mr. John Colbatch's Styptic', although effective in animals, was in fact a violent caustic (Phil.Trans. 1693-4, 18, 42). In 1724, Sprengell observed that 'Dr. Eaton's Styptic', which was prepared from 'iron and tarter', was quite ineffective and had reached England after other countries had discarded it (Phil.Trans., 1724, 33, 108).

<sup>187</sup> Statistical Essays, London, 1733, Vol.ii, p. 133.

<sup>188</sup> Ibid., p. 133.

Tables summarizing the results of experiments by  
Stephen Hales reported in his  
Statical Essays, London, 1733, Vol. ii

Table I. Experiments with Brandy

Solution	Volume (Each 18 cubic inches- 10 fl. ozs.)	Time Seconds.
Warm water 7 volumes	1st 7th	52 46
Brandy 5 volumes	1st 5th	68 72
Water 1 volume	1 volume	54

Table II. Experiments with decoction of Peruvian bark

Warm water 4 volumes	4th	62
Decoction 16 volumes	1st 16th	72 224
Warm water 11 volumes	1st 11th	198 96

continued:

Table III. Experiments with decoction of oak bark

Solution	Volume (Each 18 cubic inches- 10 fl. ozs.)	Time Seconds
Warm water 1 volume	1st	38
Decoction 6 volumes	6th	136

Table IV. Experiments with 'Piermont Water'

Warm water 12 volumes	1st 12th	68 38
Piermont water 17 volumes	1st 17th	40 76
Warm water 10 volumes	10th	68



properties. In a final experiment the effects of 'Piermont Water' (Pyrmont water), an iron-containing mineral-water, were investigated<sup>189</sup> (see Table IV).

Hales believed that the state of health depended upon an equilibrium between the solids and fluids of the body and that medicines served to compensate for any change in the solids by relaxing, contracting or strengthening them. His experiments were designed to observe these properties and so confirm "the known Explanation of the Operations of Medicines".<sup>190</sup> From the results of the investigation he concluded, in accord with his preconceived ideas, that the vessels of the body are contracted or relaxed according to the nature of the fluids passing through them.<sup>191</sup> It was assumed that these changes were greatest in the fine capillaries where there is the largest area of contact. The specific effects of the solutions tested were explained in purely physico-

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<sup>189</sup> Statical Essays, London, 1733, Vol.ii, p. 135.  
Note: Pereira in the 3rd edition of his Materia Medica (London, 1849) described Piermont (or Pyrmont) Water as a mineral water and classified as a chalybeate or ferruginous water containing carbonate of iron.

<sup>190</sup> Hales, S., Ibid., p. 126.

<sup>191</sup> Ibid., pp. 135-138.

mechanical terms. The Pyrmont Water, decoctions of Peruvian bark and Chamomile were said to attenuate or thin the blood thereby increasing its flow through the contracted vessels. This resulted in an increase of heat, which invigorated the patient and produced a 'tonic' effect. The action of brandy, which Hales refused to acknowledge as a tonic, was explained in similar terms but to produce the opposite effects. Instead of thinning the blood, brandy was said to thicken it, so setting up resistance and friction in the contracted vessels, and this, together with the effects of mixing alcohol and water, was responsible for a sudden rise in temperature (manifest in the sudden glowing warmth experienced when the spirit is swallowed). These sudden intense heat-changes resulted in a dilation of the vessels of the brain, causing intoxication and sleep. Alcoholism, according to this theory, is due to the constant contraction and relaxation of the vessels, which eventually destroys their tone so that the necessary tension can be restored only by further doses of the spirit. This argument together with a description of other chemico-mechanical effects of alcohol, e.g., its action on extravasated blood and on raw flesh, was used by Hales in temperance tracts (published anonymously) as warnings on the dangers of drinking spirits.<sup>192</sup>

Mechanical explanations of the action of drugs rarely involve questions concerning the validity of the experimental results when directly applied to practical human medicine. Thus Hales did not hesitate to apply the conclusions arising from his experiments on the vessels of a dead animal to the action of a medicine on the patient. The only difference he recognized between the reactions of his subjects and those of a live animal or man was one of degree; in the live animal the effect of the medicine would be less sudden <sup>and</sup> ~~due~~ to the dilution by the blood.<sup>193</sup>

(ii) Experiments with Cherry-laurel Water

Shortly before the publication of Hales' work there began a series of experiments with a preparation that was of particular interest to pharmacologists and toxicologists for over a century. In 1728 it was reported that two women had died in Dublin after drinking Cherry-laurel Water, an aromatic solution containing hydrocyanic acid, obtained by distilling the leaves of the

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<sup>192</sup> A Friendly Admonition to the Drinkers of Brandy, London, 1734, 2nd ed., p. 3 et seq.  
Distilled Spiritous Liquors the Bane of the Nation, London, 1736, p. 28 et seq.

<sup>193</sup> Hales, S., Statical Essays, London, 1733, Vol. 2, p. 136.

Cherry-laurel (Prunus laurocerasus, L.). This preparation was occasionally used as a medicine and commonly used for culinary flavouring or as an additive to brandy. A number of the physicians in Dublin made experiments with the suspected poison, among them Thomas Maddern (died circa 1734), a Lecturer in Anatomy and Surgery in Trinity College. In his experiments, which were published in 1731,<sup>194</sup> Maddern gave the water to dogs, and found the reactions of the animals varied with the dose. If small doses of one fluid drachm ( $\mathfrak{z}\dot{\text{i}}$ ) to half fluid ounce ( $\mathfrak{zss}$ ) were given by mouth, per anum or even by injection in the external jugular vein, the dog, although it exhibited palpitations and convulsions, eventually recovered. Larger doses ( $\mathfrak{z}\text{i} - \mathfrak{z}\text{iii}$ ) were followed by violent convulsions and paralysis, which terminated in death, the time of death varying from 2-7 minutes. Massive doses ( $\mathfrak{z}\text{v}$  to a dog the size of an Italian greyhound and  $\mathfrak{z}\text{iii}$  to a lap-dog) brought about paralysis and death but without convulsions. Maddern's post-mortem reports are of a general nature, noting little more, in the majority of cases, than that the vessels were distended with blood. In one experiment, however, where four fluid ounces had

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<sup>194</sup> Maddern, T., Phil.Trans., 1731, 37, 84.

been given per anum to a middle-sized dog, the blood was described as being of a 'very bright florid colour' and more 'florid than usual'.<sup>195</sup>

The object of these experiments was simply to prove the Cherry-laurel water a poison and they undoubtedly succeeded. Maddern made no attempt to explain the action of the substance, although he opposed the view, put forward by colleagues, that the poison caused inflammation of the stomach and intestines. He objected to this by saying that he had observed none of the symptoms usually observed with corrosive poisons and pointed out that animals, which suffered convulsions after administration of the liquor, recovered too quickly for stomach-inflammation to have been the cause of their condition. He suggested that his colleagues had mistaken for inflammation the natural ruddy colour of the stomach-lining in the dog.<sup>196</sup>

These observations were confirmed in 1731 by Cromwell Mortimer (d. 1752), then second (or acting) Secretary of the Royal Society.<sup>197</sup> He administered the distilled preparation to five dogs and in all cases he

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<sup>195</sup> Maddern, T., Phil.Trans., 1731, 37, 92.

<sup>196</sup> Ibid., p. 98-99.

<sup>197</sup> Mortimer, C., Phil.Trans., 1731, 37, 163.

observed convulsions, paralysis of the legs and difficulty of respiration. He too failed to find evidence of inflammation but commented on the bright and florid colour of the blood. In a puppy, which had been given successive quantities of the preparation, he noted that the lungs were redder than usual and the dura mater was livid: a mastiff, similarly treated, was found to have apparently inflamed lungs owing to the colour of the blood. Clots of blood found in the veins and ventricle of the heart led Mortimer to the conclusion that the poison acted by coagulating the blood, so that it could not pass the lungs and brain.<sup>198</sup> A further confirmation of Maddern's work is to be found in the report of experiments carried out under the direction of Abraham Vater (1684-1751) and published in 1737.<sup>199</sup> These investigations showed the Cherry-laurel Water to be poisonous to pigeons and the

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<sup>198</sup> Mortimer, C., Phil.Trans., 1731, 37, 170.

<sup>199</sup> Vater, A., Diss. de Laurocerasi indole venenata exemplis hominum et brutorum ejus aqua necatorum confirmata. Resp. J.A.S. Boettiger, Wittenbergae, 1737.  
quoted by Wibmer, C., Die Wirkung der Arzneimittel und Gift im Gesunden thierischen Körper. Munich, 1831-42, vol. ii, p. 82.

expressed juice of the leaves poisonous to dogs.

The toxicity having been proved, another member of the Royal Society, the physician Browne Langrish (d. 1759), attempted to look further into the mode of action of this preparation and to investigate the effects of small doses administered over a prolonged period. The work was first reported to the Royal Society in 1734 and later the experiments were included in his book Physical Experiments upon Brutes (London, 1746), a work in which he described the value and importance of animal experiments to medicine (vide infra). Langrish prepared a standard sample of the Cherry-laurel Water, using the method adopted by Mortimer. He took a peck of fresh leaves, weighing them carefully "lest I might be deceived by different measure in future Tryalls", mixing them with three gallons of water, distilling the mixture in a common alembic still, and collecting two quarts of distillate. In an initial experiment to see if the distillate had the same strength as those used by other workers, he gave four fluid ounces to a large mastiff dog. The animal became convulsed and died within the hour.<sup>200</sup> The

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<sup>200</sup> Langrish, B., Physical Experiments, London, 1746, . . . , pp. 60-61.

post-mortem examination of this animal revealed a quantity of clear viscous mucus in the stomach, and Langrish attached some significance to this observation, believing the mucus to be a coagulation of gastric juice.

Langrish made a further examination of this matter by injecting the Cherry-laurel Water into an isolated stomach immersed in a water-bath at body-temperature.

He failed, however, to obtain the mucus discovered in the first experiment and concluded that the laurel water stimulated the nerves and 'excretory ducts' (sic) in the living animal to produce a substance which enters the stomach and forms a 'bond of union' between itself, the gastric juice and the laurel water.<sup>201</sup> The toxic effects of the liquor he attributed to action on the nerves and animal spirits, the action of the poison being too rapid to be explained by any other way, i.e. by absorption into the circulation. In spite of this, in the course of his work, Langrish drew attention to the effect the preparation had upon the blood. Mortimer and Maddern had both observed changes in the colour of the blood, and Langrish

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<sup>201</sup> Langrish, B., Physical Experiments, London, 1746,  
pp. 63- 64.

<sup>202</sup> Ibid., p. 65.



confirmed this in his fourth experiment<sup>203</sup> when large doses were administered to an old horse suffering from the 'pole evil' - an inflamed or ulcerous sore between the ligaments of the neck and the atlas bone. Before the first dose of one pint was administered, blood taken from the jugular vein was described as "viscid and foul". Afterwards it was described as "improved in colour" and such was the improvement after subsequent doses that Langrish concluded the liquor to have the effect of attenuating, dividing and altering the "Arrangement and cohesion of the particles of .... viscid, strong foul Blood".<sup>204</sup> During this experiment the Cherry-laurel Water appears to have had a therapeutic effect, temporarily stemming the discharge from the ulcer. Another example of this appears in a later experiment, when the preparation was given to a young horse with glanders, an infectious disease marked by purulent inflammation of mucous surfaces. Langrish recorded, in this case, that a foul yellow nasal discharge became white "well digested" and odourless.<sup>205</sup>

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<sup>203</sup> Langrish, B., Physical Experiments, London, 1746,  
pp. 68-73.

<sup>204</sup> Ibid., p. 73.

<sup>205</sup> Ibid., p. 106.

Further effects upon the blood were observed in experiments with small 'non-toxic' doses on dogs which were carried out in the latter half of 1733. In these investigations, Langrish endeavoured to follow the changes in the system by measuring (a) the pulse rate and (b) changes in the blood itself by separating and weighing serum from samples drawn from the jugular vein. To the first animal he gave a dose of  $\text{℥ i}$  (one drachm or 60 minim) for a month, then increased the dose to  $\text{℥ iss}$  and, after another month, increased it to  $\text{℥ ii}$ . He noted, during the course of this experiment, that the pulse rate increased from 78 to 135 per minute and, at the end of the third month, the blood was "extremely florid and beautiful ... the Coagulum ... as vivid as possible".<sup>206</sup> The subject of this experiment remained apparently healthy and even grew fat. Langrish, therefore, concluded this dose to be beneficial and its action to be due to its ability to thin the blood and so increase the circulation, i.e. to the 'tonic' effect (vide Hales). In another experiment<sup>207</sup> the dose was increased from

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<sup>206</sup> Langrish, B., Physical Experiments, London, 1746,  
p. 74 et seq.

<sup>207</sup> Ibid., p. 82 et seq.

3 ii to 3 iv over approximately the same period, and the same observations were made on the blood and pulse-rate. In this case, however, the animal sickened when the higher dose was reached. The third experiment in this series, performed at the same time as the other two, consisted in administering doses of the fresh leaves, beaten fine and wrapped in food. The results are summarized in Table V. The increase in the weight of separated serum confirmed the opinion Langrish held that the principles contained in the leaves attenuated or thinned the blood.<sup>208</sup>

This 'attenuation' of the blood was attributed to alterations brought about in the cohesion of the particles of that fluid. In 1734 Langrish investigated this matter further by measuring the resistance of the blood-clot which is formed when the sample is allowed to stand. The technique was as follows: he took a glass tube, 1/3 inch diameter, with a closed 'obtuse' point about the size of a pea; this was rested on the clot or 'crassamentum' formed after the blood had been left to stand for 24 hours; and mercury was poured into the tube

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<sup>208</sup> Langrish, B., Physical Experiments, London, 1746,  
p. 95 et seq.

Table V. Summary of the results obtained by Langrish after feeding Cherry-laurel leaves to a dog. Physical Experiments, London, 1746, p. 95.

Date (1733)	Dosage	wt. of serum in 3 iiss of blood	Other Observations
Aug. 4th	-	3 v grs.50	pulse 83-4
Aug. 18th	3 ii over 14 days	3 vi grs.24	pulse 85-100
Sep. 1st	3 iv over 12 days	3 vi grs.40	serum ruby colour blood clot - vivid
Sep. 15th	3 vi over 15 days	3 vii grs.36	dog healthy, pulse same
Sep. 29th	3 i over 14 days	3 vii grs.25	health declining, pulse 120-130
Oct. 13th	3 i 3 ii over 15 days	3 vii grs.55	Blood clot - florid, Dog losing weight
Oct. 27th	3 i 3 iv over 14 days	3 vii grs.45	-
Nov. 10th	3 i 3 vi over 14 days	3 vi grs.56	pulse full and quick
Nov. 24th	3 ii over 14 days	3 vi grs.40	Blood clot described as 'no vermillion could be a more lively colour'. Pulse 157 Dog obviously sick.
Dec. 1st	3 iiss over 7 days	-	-
Dec. 15th	3 iii for 6 days after this administration difficult and exp't abandoned	3 v grs 30	Dog very ill

Note: 3 i = one drachm = 60 grains. 3 i = one ounce = 480 grains

until the point penetrated the mass. The height of the mercury column was taken to be proportional to the resistance. The experiment was made on the blood of a young horse sick with glanders<sup>209</sup> and the results are summarized in Table VI. It will be seen that the reported resistance of the blood-clot in the early stages of the experiment is extremely high but that it dropped after the administration of the Cherry-laurel Water. The results of this experiment again confirmed the theory of the attenuating effect of this preparation on blood.

Earlier observations on the pulse rate had suggested to Langrish that there was an increase in the rate of circulation. Hales had suggested that this resulted from a thinning of the blood and a contraction of the vessels. It was, therefore, natural that Langrish should next determine if the Cherry-laurel Water affected the blood vessels as well as the blood itself. To do this he repeated in detail the experiment of Stephen Hales, whom he described as "my very ingenious Friend". He found that blood-warm water took 75 seconds to pass through the tube and vessels, but after

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<sup>209</sup> Langrish, B., Physical Experiments, London, 1746,  
p. 103.

Table VI. Summary of results obtained by Langrish  
after administering large doses of  
Cherry-laurel Water to a young horse.  
Physical Experiments, London, 1746, p.103.

Date (1734)	Dosage (over 8 days)	Volume of Blood	Weight of serum	Height of mercury in inches req'd to break through the surface of the blood-clot.
July 28th	-	℥viii	℥ii grs.10	13½
Aug. 5th	℥vi	"	℥i grs.120	13½
Aug.13th	℥viii	"	℥i grs.240	10
Aug.21st	℥xii	"	℥i grs.270	7¼
Aug.29th	℥xx	"	℥i grs.360	4

four successive volumes of Cherry-laurel Water the time increased to 105 seconds. He entertained no doubts that similar effects would take place in the living body after absorption, and wrote "it evidently appears that Laurel-Water greatly contracts the lifeless Fibres, and how much more they answer to any Impulse when animated, every one who is acquainted with the Animal Oeconomy must needs understand".<sup>210</sup>

When one surveys this work, the only general conclusion to be drawn is that it demonstrated the toxic effects of Cherry-laurel to be dependent upon the dose administered. Taking the same broad view, it must be admitted that in respect of general medicine the conclusions were detrimental, for, by believing that the effects on the blood were 'tonic' and beneficial, in particular the 'improved' colour (due to the formation of cyanmethaemoglobin), Langrish encouraged its administration in toxic and near-toxic doses. In spite of this there are a number of interesting features in this work. First Langrish appreciated the value of animal experiments to the progress of medicine and realized that, in the

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<sup>210</sup> Langrish, B., Physical Experiments, London, 1746,  
p. 115.

investigation of any substance even of a reported poison, it is important to investigate the effects of small doses over a long period as well as the effects of large toxic doses. With the Cherry-laurel he showed that the effects in the two cases were quite different. (Later in the century, by using smaller doses, Stoerk and Withering redeemed the therapeutic reputations of Colchicum and Digitalis.) The state of knowledge concerning the action of drugs when Langrish was writing was such that it is not surprising that he attributed the different effects of large and small doses to different causes, the former by direct action through the nerves and the latter by action on the blood after absorption. In addition to emphasizing the importance of the dose, he also drew attention to the fact that the properties of a drug depend partly upon the mode of administration. He realized the possibility of errors arising from experiments where the substance is directly injected into the blood, observing that injection of the most innocuous liquids was known to cause distress and uneasiness. He directed that care must be taken when comparing the results of medicines injected and of medicines ingested since in the latter case:

"considering how gradually any Medicine  
is imbibed and blended with the Blood, when



taken by the Mouth, it evidently appears that its Effects will be in Proportion to the Commixture".<sup>211</sup>

Another important feature of this work was that Langrish followed the example of Hales and applied quantitative techniques to study physiological changes, i.e., his measurement of the blood serum and the resistance of the clot. It should be noted that in all experiments tests were made upon blood taken from a living animal under the influence of the poison. Langrish could see no value in attempting to study the action of a substance by adding it to the extravasated blood after the manner of Slare.<sup>212</sup>

The suggestion, in Langrish's work, that Cherry-laurel Water might have some tonic effect did not result in its recommendation for general practice. This was because the reports of its toxicity, which Langrish himself confirmed, were so emphatic that they not only proscribed the Water itself but also preparations having a similar odour and flavour, e.g., 'almond water' prepared by distillation of bitter almonds.<sup>213</sup> The

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<sup>211</sup> Langrish, B., Physical Experiments, London, 1746, p. 59.

<sup>212</sup> Ibid., p. 107.

<sup>213</sup> Pemberton, H., Dispensatory, London, 1746, p. 77.

effect of these experiments is significant in the case of Aqua cerasorum nigrorum (Black cherry water), prepared by the distillation of cherry stones. This preparation was deleted by the revision committee of the 5th edition of the London Pharmacopoeia, notwithstanding the fact that it was then a common remedy and the recognized treatment for 'convulsive fits' in children.<sup>214</sup> Members of the Committee together with other physicians made experiments on animals and found it to have similar effects to the Cherry-laurel.<sup>215</sup> In giving its reason for the deletion the Committee pointed out that, although the preparation might well be safe for adults in moderate doses, it was most certainly dangerous to children, especially in the hands of unskilled nurses.

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<sup>214</sup> A Draught for the reformation of the London Pharmacopoeia, prepared for the purusal of the Members of the College of Physicians, by their Committee appointed to that purpose. London, 1742, p. ix.

<sup>215</sup> No details of the experiments are given in the Draught or in Pemberton's Dispensatory. In 1741 in London, an anonymous work was published entitled Experiments with Almond Water and Black Cherry and it is reasonable to suppose that this book (or tract) contained reports of experiments which confirmed the Committee in their decision. Waring, who lists the work (Bibliotheca Therapeutica, London, 1878, Vol. I.

(iii) Experiments with Arrow Poisons

The arrow poisons aroused considerable interest in the eighteenth century and reports of their rapid action and toxicity resulted in a number of animal experiments. The use of the poisoned arrow for hunting game and as a weapon of war was the independent discovery of primitive peoples in many different parts of the world. Natives of the Congo and East Africa used extracts prepared from a species of *Strophanthus*, which contains the glycoside oubain (*strophanthia-G*); in Western and Central Asia, poisons containing the alkaloid aconitine were prepared from Aconite: in the Malayan Archipelago, arrows were tipped with a substance containing strychnine and the Indians of South America used curare extracts. Not all the poisons used were of vegetable origin, the Hottentots of South Africa, for example, are reported to have smeared their weapons with snake venom.<sup>216</sup>

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p. 227), notes that it is in the library of the London Medical Society. Unfortunately, there is no trace of the work in that collection. Efforts to trace the book in other libraries have also failed.

<sup>216</sup> The nature of geographical sources of arrow poisons ~~have~~<sup>has</sup> been extensively studied by L. Lewin, Die Pfeilgifte, Leipzig, 1923, and Perrot & Vogt, Poisons de Flèches et Poisons d'Épreuve, Paris, 1913.

In the seventeenth century members of the Royal Society made experiments with an arrow poison described as the Macassar poison, which may have been one of the Malayan strychnine extracts. Although the manner of its use was communicated to the members, they failed on two occasions to harm a dog by wounding it with an instrument smeared with the substance.<sup>217</sup> Fontana was later to show that experiments of this type often failed either because the poison was not allowed to dry on the weapon so that it was deposited on the skin or because instant and excessive bleeding carried it away from the wounded tissues.<sup>218</sup> It is possible that this Macassar poison was that same 'Indian poison' shown to Boyle, who was told that the time of death depended upon the distance of the wound from the heart.<sup>219</sup>

In the first half of the eighteenth century, attention was directed to the arrow poisons of South America. Many travellers to that continent had reported upon the poisons used by the Indians, although their

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<sup>217</sup> Birch, T., History ..., London, 1756, Vol. ii, pp. 23, 318; Phil.Trans., 1666, I, 417.

<sup>218</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p.91.

<sup>219</sup> Boyle, R., Experimental Naturall Philosophy, Oxford, 1664 (2nd ed.), part II, p. 51.

stories varied considerably. The Jesuit, Cristoval D'Acuña,<sup>220</sup> for example, reported death from the poison to be sudden, following immediately upon the wound. Sir Walter Raleigh,<sup>221</sup> on the other hand, said that death intervened only after hours of torment. The differences in these reports were due to the variation in composition and concentration of poisons used by the different tribes. All reports agreed at least that the poisons brought about an immediate effect and were eventually fatal. Experiments to confirm these reports became possible when the travellers and explorers brought to Europe not only reports but also samples of the arrow poisons. One of the first to do this was the French scientist and explorer, de La Condamine.

Charles-Marie de La Condamine (1701-1774) was a member of the French Académie<sup>of Sciences</sup> and went with others to South America to study the earth's oblateness<sup>ness</sup>. On the completion of their work, the members of the team chose

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<sup>220</sup>Cristoval D'Acuna, Nuevo descubrimiento del gran rio de las Amazons, Madrid, 1641, p. 17.

Translated in Markham, C R., Expeditions into the valley of the Amazons, London, Hakluyt Soc., 1859, p. 81.

<sup>221</sup> Raleigh, Sir Walter, The Discoverie of Guiana, London, 1596, p. 59.

different routes for the homeward journey. La Condamine decided to follow the course of the Amazon and left Tarqui (Peru) in May, 1743. During the course of his long journey he made a number of valuable and interesting observations, which were reported to the Académie on his return.<sup>222</sup> On several occasions during the journey he ate game killed by his Indian guides with poisoned arrows and he discovered that the poison was effective only when shot into the flesh, neither the meat of the animal killed by the arrow nor the poison itself being dangerous when eaten.<sup>223</sup> The poisons used by these guides were curare extracts and La Condamine succeeded in obtaining samples prepared by the Ticuna Indians.<sup>224</sup>

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<sup>222</sup> La Condamine, Mém. Acad. R. Sci., 1745 (pub. 1749), 391

On this journey the explorer made an unsuccessful attempt to preserve seeds and seedlings of the medicinally valuable Quinquina (cinchona) for cultivation in France.

<sup>223</sup> Ibid., p. 425.

<sup>224</sup> Curare is a generic term applied to a number of South American arrow poisons. A true curare, in the scientific sense, is a mixture of curare alkaloids, usually prepared from the bark of the Strychnos toxifera and other species of Strychnos. They cause muscle paralysis on injection. A great number of the South American poisons are true curares, although

During a stay at Cayenne, while awaiting a ship to take him home to France, La Condamine decided to make some experiments with the arrows, the primary purpose being to see if the poison had retained its potency. Before an audience composed of the Governor, officers of the Garrison and the King's physician, he slightly wounded a pullet with one of the arrows. The animal died within seven minutes. He repeated the experiment, but for this second test he dissolved some of the poison in water and dipped the arrow into the solution. After one minute the animal was seized with convulsions and died in spite of attempts to save it by administering sugar - a reputed antidote for the poison. In a third experiment, sugar was administered immediately after the wound was made and the animal survived.<sup>225</sup> Later, however, on 23 January 1745, when La Condamine repeated these experiments at

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their composition and preparation differ from tribe to tribe. In the extensive literature these poisons appear under many names. In the early work they were named after the tribe or area from which they came, e.g., the poison of Ticunas. In later literature they appeared under a number of variants of the word curare, e.g., uirari, wourali, woorara.

<sup>225</sup> La Condamine, Mém. Acad. R. Sci., 1745 (pub. 1749), p. 489.

Leyden before Professor Musschenbroek, Van Swieten and Albinus, the sugar failed to act and the animal, to which it was administered, survived only a little longer than the others.<sup>226</sup>

The physicians of the eighteenth century were not strangers to travellers' tales of prodigious poisons that kill on a pin-prick or by mere exhalation, and a suspicion that La Condamine had been biased in his reports from a "love of Prodigy and Wonder" induced Richard Brocklesby (1722-1797) to put the poison to further tests. Brocklesby, who had graduated M.D. at Leyden in 1745 and was elected F.R.S. in 1746, communicated the results of his experiments with arrow poisons in a letter to the President of the Royal Society in 1747.<sup>227</sup>

Brocklesby used a sample of the poison brought from South America by Don Antonio de Ullõa (1716-1795),<sup>228</sup> and the manner in which this sample came into the possession of the Royal Society is worth recalling. In 1735, Ullõa, then a young officer of the Spanish Navy, was sent to assist the French astronomers in their researches in

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<sup>226</sup> La Condamine, Mém. Acad. R. Sci., 1745 (pub. 1749), p. 489.

<sup>227</sup> Brocklesby, R., Phil.Trans., 1747, 44, 408.

<sup>228</sup> The title to Brocklesby's letter in the Phil.Trans.



~~their researches in~~/South America. On his return home ten years later, he was taken prisoner by the British off Cape Breton and brought to England. In London he was treated with respect and the Lords of the Admiralty restored his papers and belongings to him. An abstract of his researches was prepared and communicated to the Royal Society and, as a result, he was elected a Fellow. In gratitude, on his eventual return to Spain, he sent some books to the President and with them samples of the celebrated arrow poisons.

Brocklesby began by making a saturated solution of the poison, and sprinkled it on a superficial wound in the nose of a cat. After fifty minutes the animal became sleepy and was convulsed, and the limbs appeared flaccid; and in this condition, says Brocklesby, the animal "expired". He removed the head and examined

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(1747 , 44, 408) is incorrect. It refers to 'the Indian Poison, sent over from M. de la Condamine'. The title should have read: " ... the Indian Poison, sent over by Don Antonio de Ullõa of Seville, F.R.S., and mentioned by M. de la Condamine .... in his late Account of the River of the Amazons in South America". See Phil. Trans., 1747, 44, Advertisement, opp. p. 566

the brain and nerves without observing any change in their appearance. On opening the thorax, however, he was surprised to find the heart still pulsating, which it continued to do for some time afterwards.<sup>229</sup> This led him to suspect that, had he not removed the head, the animal might have recovered. He decided, therefore, to repeat the experiment using a young dog. This animal exhibited the same symptoms, and, after a time, became insensible to all external influences. Brocklesby wrote "in this comatose Way he [the dog] continu'd near four Hours and then shook off his Stupor, and was much better"<sup>230</sup>

In a third experiment, using the same animal, the poison was dropped into an incision of the crural vein. Although the dog was convulsed and died within twenty minutes, no physical changes were observed in a post-mortem examination of the body. Two experiments with birds completed the work. In the first the poison was dropped into a cuticular wound made in a 'small bird' and resulted in insensibility after ten minutes and death after fifteen. To the other bird Brocklesby administered two drachms of sugar before

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<sup>229</sup> Ibid., p. 409.

<sup>230</sup> Ibid., p. 410.

introducing a few drops of the poison into its mouth. In spite of the supposed antidote, the bird was immediately convulsed and "all Motion was taken away".<sup>231</sup>

Brocklesby draws but two conclusions from his experiments. First he said that from the experiments he found that the 'supposed Specific' (i.e. the antidote sugar) is of no value. It is, of course, true, although we must observe that the sugar was used in only one of the five trials and then under the unusual condition of the poison being administered by mouth. The second conclusion was as follows:-

" ..... from them [the experiments] it may appear probable, that our Poison is nearly upon the same Footing with white Arsenic in the cure of the Tooth-ach".<sup>232</sup>

This vague analogy to a traditional and doubtful remedy indicates that Brocklesby entertained doubts concerning

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<sup>231</sup> Ibid., p. 411.

<sup>232</sup> Ibid., p. 411. Note. Arsenic in various forms is reported to have been used in dentistry by the Chinese, the Greeks, the Arabs and Mediaeval European physicians (Guerini, V., A History of Dentistry, Philadelphia, 1909, pp. 35, 85, 138, 152, 157). One of its uses was to pack it into a hollow tooth where, by cauterizing the decayed pulp, it relieved toothache

the reports of the <sup>virulence</sup> ~~(virility)~~ of the arrow poisons. This interpretation is supported by his remarks at the beginning of his letter, where he not only implies that La Condamine was exaggerating its effects but also attributes the greater number of reported poisons and antidotes to authors who raise wonder and astonishment by ascribing to the substance properties "which never existed in nature".

These conclusions were drawn because, in his experiments, Brocklesby had found that the poison was not so devastating in its effects as he had been led to believe. First, some appreciable time was found to elapse between the administration and the appearance of the effects, an observation not compatible with stories of animals being brought down in flight. Second, animals under the influence of the poison were found to recover and, in the mind of Brocklesby and his contemporaries, the virulence of a poison was measured by its ability to kill swiftly and efficiently. Thus, from the evidence of these experiments the arrow poisons did not appear to be as effective as oil of tobacco or the viper

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but not without some considerable pain beforehand. The practice was revived in the 19th century when arsenic was sealed into the tooth with mastic. Pereira described it as a painful and dangerous remedy (Materia Medica, London, 1849, 3rd ed., Vol. i, p. 666).

bite. The reason for Brocklesby's observations might be attributed to the strength of the solution used or possibly to his mode of administering the poison. In the experiment where the animal recovered, the solution was sprinkled upon a superficial wound whereas La Condamine had used the original arrows and inserted them into the flesh.

The object of these experiments was to prove the substance to be a rapid and effective poison. It is, therefore, not surprising that Brocklesby failed to see the significance of the experiment that demonstrated that the substance caused an extreme paralysis and stupor from which the animal could recover with no ill effects. In fact, in his second experiment, he used what in modern medicine would be known as a 'curarizing dose'. It was an effect not unknown, however, to the Indians themselves, who are reported to have used smaller doses when they wanted enemies to fall alive into their hands.<sup>233</sup>

Brocklesby's few experiments and depreciatory comments were overshadowed three years later by a report of over one hundred experiments with Ticunas and Lamas arrow poisons by the French anatomist

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<sup>233</sup> Schenk, G., Book of Poisons, London, 1956, p. 42.

François-David Hérissant (1714-1773).<sup>234</sup> The samples of poison he used were given to him by La Condamine and he described them as resembling Spanish liquorice in colour, consistence and smell. The experiments were made on a very wide range of subjects including mammals, birds, fish, reptiles and insects (see Table VII). His methods were simple: first the poison was prepared after the manner of the Indians by dissolving in water and evaporating to the consistence of a soft extract. It was applied to a wound soaked on a piece of cotton wool or, alternatively, by dipping an arrow or lancet into the extract, allowing it to dry and then using the instrument to stab the animal in the leg or some other fleshy part.

Hérissant was unable to demonstrate that the poison had any effect upon fish, reptiles or insects,<sup>235</sup> but with the quadrupeds he showed its effects to be as sudden and violent as La Condamine had described. In the first experiment he made a wound a quarter of an inch in length on the left hind-leg of a rabbit and applied a pledget of cotton-wool soaked in the poison. He reported that the animal died instantly before even a bandage

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<sup>234</sup> Hérissant, F.D., Phil. Trans., 1751, 47, 75.

<sup>235</sup> Ibid., p. 83.

Table VII. Table to show the animals used by  
Hérissant in experiments with curare  
arrow poisons. (Phil. Trans, 1751, 47,  
81-90)

Date (1748)	Number of Experiments	Animal
June 6th	13	Rabbits, Dogs.
" 7th	16	Rabbits, Dogs.
" 8th	1	Cat.
" 9th	Number not specified Subjects indicate a large number of trials.	Insects (caterpillars bees, flies, butter- flies, may-flies). Reptiles (vipers, other snakes, earthworms) Fish (carp, eel, pike, gudgeon, barbel, tench).
" 10th	1	Cat.
" 12th	5	Cats, Dogs.
July 15th	Number not specified Report indicates at least 20 trials	Birds (Hawk, pigeons, hens, blackbirds, sparrows, ducks, geese, magpies).
July 16th- 19th	4	Cat, Dogs, Lamb.
July 20th	1	Rabbit.
" 22nd	1	Cat.
" 24th	Number not specified	Dogs, Cats, Foxes, Horses.
" 30th	Number not specified but reference is to 'a great number'.	Rats, Mice, Moles.
August 6th	3	Pig, young Wolves.
" 7th	6	Dogs (puppies).
" 10th- 12th	Number not specified	Dogs, Cats, Pole- cats, Guinea pigs.
" 15th	6	Horses.
" 18th	1	Bear.
No date given	1	Eagle.

could be applied. The experiment was repeated with eight rabbits and four dogs, all dying within a minute. In subsequent experiments with a poisoned lancet, cats survived only three minutes, rats, mice and small birds died in less than one, horses died after eight minutes and a bear after five.<sup>236</sup>

On the second day of his experiments Hérissant compared the action of the arrow-poisons with other known toxic substances. Each was tested in the same way, by applying it on cotton-wool to a small wound in the leg of a rabbit. The poisons studied were opium (in alcoholic solution), arsenic, essential oil of Cherry-laurel, extracts of henbane, nightshade (*belladonna*), tobacco and white hellebore (*veratrum album*). No effects were observed from these poisons except from the extract of hellebore, which brought about some form of temporary derangement, described as a "sudden fit of fury".<sup>237</sup>

Hérissant, in a number of experiments, made careful observations on the symptoms of curare poisoning. He noted the gradual development of paralysis in dogs

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<sup>236</sup> Hérissant, F.D., Phil. Trans., 1751, 47, . 81, 84, 87, 90.

<sup>237</sup> Ibid., p. 81.



and cats after the administration of the poison, most noticeably in the limbs and muscles of the neck.<sup>238</sup> Later rats and mice were seen to undergo a fit of shivering followed by a general paralysis.<sup>239</sup> Of greater interest is the report of an experiment with a horse, which described the development of respiratory paralysis with irregular diaphragmatic movement. The observations were made in the period of eight minutes between the administration of the poison and the death of the horse. The first symptom was the alternate contraction and relaxation of the wounded muscle. The animal became restless and after two minutes respiration became laboured and difficult; then followed a weakness and paralysis of the limbs which led to the collapse of the animal. By this time it appeared to be insensible to the pain of the whip and its respiration was laboured:-

"each inspiration consisted of three successive attempts, and then followed a most precipitate expiration, accompanied with so violent hiccup, that, the body bending double, the hind legs were pulled quite to the fore-legs." <sup>240</sup>

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<sup>238</sup> Hérissant, F.D., Phil.Trans., 1751, 47, 83-4.

<sup>239</sup> Ibid., p. 86, <sup>240</sup> Ibid., p. 88.

In the post-mortem examination he notes particularly that the muscles are flaccid and cold or 'clammy' to the touch, a condition he suggested to be indicative of poisoning with the South American arrow-poisons. An even more dramatic description of death by asphyxiation resulting from respiratory paralysis is given in his report of the experiment with the bear which is said to have died in less than five minutes, "having his throat squeezed, as if he had been strangled".<sup>241</sup>

When, after his early studies, he had confirmed that the action was both swift and fatal, Hérissant began a series of experiments to find an antidote or a means to prevent the development of the symptoms. In his experiment with birds he repeated the experiments of La Condamine, administering both salt and sugar, but to no effect. He then turned to methods designed to prevent the poison entering the circulation. In the first attempt he wounded a rabbit in the paw, inserted the poison and immediately amputated the foot above the wound. The animal survived. The experiment was successfully repeated with two dogs and a lamb.<sup>242</sup>

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<sup>241</sup> Hérissant, F.D., Phil. Trans., 1751, 47, . 90.

<sup>242</sup> Ibid., p. 85.

The next step was to apply a ligature above the wound before applying the poison. Unfortunately, the experiment failed, the animal dying within two minutes of the poison being applied. As a result the idea of the ligature was not followed up; instead, attention was given to destroying the poison by cauterization. Dogs, cats, foxes and horses were wounded, the poison was introduced, and then the wound was immediately cauterized by means of a red-hot iron or by burning charcoal. All the animals survived.<sup>243</sup>

These experiments of Hérissant are of particular interest in the history of curare for the following reasons:-

(i) They showed that the action of the poison was both swift and fatal, thereby confirming reports that they were effective in the hunting of game. Hérissant went further; he and his friends ate the flesh of rabbits used in the experiments and so confirmed La Condamine's story that the flesh of game hunted with poisoned arrows is harmless.<sup>244</sup>

(ii) The poison was tested on a wide variety of

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<sup>243</sup> Hérissant, F.D., Phil. Trans., 1751, 47, .. 86

<sup>244</sup> Ibid., p. 81.

species and was shown to be universally fatal to mammals and birds.

(iii) The action of the arrow-poison was compared with the action of other poisons administered in the same way.

(iv) The symptoms of poisoning were observed and carefully described. Hérissant noted that death is apparently painless and preceded by a universal and sudden paralysis. He did not appreciate the exact cause of death, although in some of the experiments he carefully described asphyxiation and other symptoms of respiratory paralysis.

(v) The supposed antidotes, salt and sugar, were shown to be ineffective, as he put forward the view that the action of the poison was too quick to allow time for any specific given by mouth to act. On the basis of his experiments he recommended the use of the cautery as the most effective remedy, but emphasized that it must be swiftly applied.

Although at the time Hérissant was writing it had been suggested that the action of rapidly acting poisons could be explained only by a direct effect through the nerves, he had no doubt but that the poison acted through the circulation. He believed that it was

absorbed into the circulation from the wound and carried to those parts it must effect in order to cause death. The length of time between administration and death was held to be proportional to the amount of poison entering and mixing with the blood.<sup>245</sup> He did not venture further than this in his explanation of the mode of action. In his conclusions he noted that the colour of the blood is altered in some animals, but declined to infer that the poison acts directly on the blood partly because it was not found to occur in all cases. No experiments were specifically designed to confirm the theory of action through the circulation, but one at least clearly demonstrated that the poison acted swiftly only if it entered the blood stream directly through a wound. The principal object of this experiment was to observe the effect when the poison was in direct contact with the abdominal viscera. Hérissant made an opening in the abdominal wall of a cat and, with the aid of a funnel, poured half a drachm of the solution into the cavity over the viscera, taking extreme care to ensure that none of the substance came into contact with the lips of the wound. The animal survived an hour. According to Hérissant its

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<sup>245</sup> Hérissant, F.D., Phil. Trans., 1751, 47, . 89-92.

eventual death was due to convulsions of the throat, so that it was unable to breath.<sup>246</sup>

It was unfortunate that, although Hérissant believed the period of onset of symptoms to be dependent upon the amount of poison entering the circulation, he made no attempt to relate the effects to the quantity administered and it was left to Fontana (vide infra) to make experiments using different doses of the poison. It was also unfortunate that in some of his work he omitted to use control experiments. This is particularly obvious in the experiment where he tried to poison animals with the blood taken from the vena cava of a dog previously killed with a mixture of the Ticunas and Lamas poisons. Seven or eight drops of the blood were instilled into wounds in dogs, cats, pole-cats and guinea pigs. The animals all survived but were said to have become indisposed and sullen and to have lost their vivacity. After eight days, more blood was administered and the animals became weak and faint. The following day more blood was instilled and the animals died in four to five days.<sup>247</sup> Without control experiments it would be

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<sup>246</sup> Hérissant, F.D., Phil. Trans., 1751, 47, : 83.

<sup>247</sup> Ibid., pp. 86-7.

difficult to decide if the animals died as a result of the poisons or of the wounds themselves. Hérissant himself does not comment on the result. It is, in fact, one of the disappointing features of Hérissant's report of his work that, on a number of occasions, he allowed results to pass without comment. He made no attempt, for example, to explain the failure of the ligature experiment. It is true that the purpose here was a practical one and he possibly reasoned that, if the ligature was ineffective if applied before the poison was administered, it would most certainly be valueless if applied after. Nevertheless, he appears to have made no efforts to repeat the experiment, although the successful amputation experiments were repeated several times. Hérissant's tendency to leave 'loose ends' and refrain from comment was on one occasion at least to lead to misinterpretation. He made an experiment in which he shaved the hair off an area of the skin of six puppies and rubbed this part with poison. All the puppies died.<sup>248</sup> He made no attempt, however, to explain the death of the puppies and one is left to assume that this was due to

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<sup>248</sup> Hérissant, F.D., Phil. Trans., 1751, 47, 86.

absorption through the unbroken skin. Now Hérissant knew that this was not possible, because when he was preparing the poison a bottle exploded and its contents were spilt over his hands and arms. Commenting on this, he remarked on his good fortune that the skin was unbroken and, therefore, the poison ineffective.<sup>249</sup>

It is almost certain that the skin of the puppies was broken probably by the process of shaving, but there is no indication of this in the report and the result stands in contradiction to the earlier statement.

Hérissant's experiments do not provide a perfect model for experimental pharmacology. Nevertheless, for the reasons given, they were a landmark in the pharmacology of curare and the most extensive before the work of Fontana. It is interesting to note that he found a use for the poison after observing it to kill animals without apparent surface damage to the body. When a friend, M. le Chevalier de Grostée, had an eagle which he wished to present to Réaumur for his natural history cabinet, Hérissant, using the arrows, was able to kill it without any damage to the feathers. They were used for the same purpose on a bear.<sup>250</sup>

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<sup>249</sup> Hérissant, Phil. Trans., 1751, 47, 79.

<sup>250</sup> Ibid., p. 90.



(iv) Experiments with Opium

Opium is one of the most ancient of anodynes and its narcotic properties are referred to by Pliny,<sup>251</sup> Celsus,<sup>252</sup> Dioscorides<sup>253</sup> and Galen.<sup>254</sup> It was a valued constituent of several of the more favoured Galenical remedies and in 1589, in one of the earliest references to the proposed Pharmacopoeia Londinensis, the electuaries were sub-divided into *Electuaria* and *Opiata*.<sup>255</sup> In the seventeenth century the drug was widely prescribed and Sydenham regarded it as one of the few really useful drugs in the *materia medica*.

It was inevitable that for a drug so widely used and discussed some considerable knowledge accumulated concerning its action upon the body. Seventeenth-century physicians were well aware that it acted

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<sup>251</sup> Pliny, Natural History, Bk. xx, 76. (Loeb Classical Library, London, 1951, Vol. 6, p. 114).

<sup>252</sup> Celsus, De Medicina, Bk. v, 23, 25. (Loeb Classical Library, London, 1953, Vol. 2, pp. 54).

<sup>253</sup> Dioscorides, Bk. iv, 65. (from Gunther, R.T., The Greek Herbal of Dioscorides, Oxford, 1934, p.456).

<sup>254</sup> Galen, Opera Omnia, Edit. C.G. Kühn, Lipsiae, 1821-33, Vol. xiii, 273.

<sup>255</sup> Urdang, G., History of the Pharmacopoeia Londinensis, Madison, 1944, p. 11.

as a poison as well as a medicine<sup>256</sup> and, at the beginning of the eighteenth century, Dr. John Jones, Chancellor of the Cathedral Church at Llandaff and licentiate of the College of Physicians, was able to catalogue the effects of opium given in both moderate (1-3 gr.) and immoderate doses. In the same work he described the miseries of addiction, in particular the effects of sudden withdrawal, which causes "Great and even intolerable Distresses, Anxieties, and Depressions of Spirits ..." <sup>257</sup> A number of comprehensive dissertations on the drug appeared in the seventeenth and eighteenth centuries in most cases concerned with the source, preparations and use in medical practice.<sup>258</sup> Many of

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<sup>256</sup> See Gerarde, J., Herball, London, 1633, p. 400.  
 Parkinson, J., Theatricum Botanicum, London,  
 1640, p. 368.

<sup>257</sup> Jones, J., The Mysteries of Opium Reveald, London, 1700, pp. 20, 29, 30 et seq.

The catalogues of effects are alone useful in this verbose work which Munk declared to be "extraordinary and perfectly unintelligible" (Roll, London, 1878, Vol. i, p. 476).

<sup>258</sup> Waring in the Bibliotheca Therapeutica (London, 1878) lists 29 publications on opium in the 17th century and 75 in the 18th. This list is by no means exhaustive and omits a number of lengthy dissertations appearing in Journals.

these were engaged in controversies concerning the therapeutic use of the medicine, e.g., its use in inflammations. It was inevitable that a drug of such interest should become the subject of a number of animal experiments and these increased in<sup>like</sup> eighteenth century as a controversy developed concerning its mode of action and its effect upon the nerves and heart.

a. Experimental studies on opium before 1750

In the seventeenth century the effects of the oral administration of opium on animals were examined by Courten and Mead,<sup>259</sup> while those of injection into the veins of dogs were studied by Wren,<sup>260</sup> Elsholz,<sup>261</sup> Major<sup>262</sup> and Abrahamson.<sup>263</sup> In 1703 Christoph Fimmlerus reported the effects of administering half a scruple (10 grains) to a cat and two drachms (120 grains) to a dog. In both cases he observed an initial narcosis

<sup>259</sup> See p. 49 above.

<sup>260</sup> p. 43 above.

<sup>261</sup> Elsholtz, J.S., Clysmatica Nova, Coloniae Brandenburgicae, 1667, p. 14.

<sup>262</sup> Wibmer, C., Die Wirk. d. Arzneim. u. Gifte, Munich, 1831-1842, Vol. 4, p. 74.

<sup>263</sup> . . . Ibid., Vol. 4, p. 75.

followed by convulsions and death.<sup>264</sup> In 1730 Caspar Neumann (1683-1737) reported that a few grains of the resinous substance extracted from the drug by alcohol and water killed a dog which had survived a dose of one drachm of the crude drug.<sup>265</sup> Further experiments administering resinous and gummy 'constituents' of opium were reported in 1748 by Christian Schwartz,<sup>266</sup> a student of Andrea Büchner (1701-1769) in Halle. In this work the products of distillation and extraction were administered to dogs in doses of 40 grains. The invariable results of these experiments were convulsions terminating in death.

A series of experiments of greater interest and with improved technique were made in 1732 by Charles Alston (1683-1760), at one time a student of Boerhaave, Lecturer in Botany and Materia Medica in Edinburgh. One of the principal points of interest in early

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<sup>264</sup> Fimmlerus, C., Diss. de vi opii rarefaciente . . ., Praes. J.G. Bergeri, Vitembergae, 1703, pp. 9-11.

<sup>265</sup> Neumann, C., Lectiones Publicae, Berlin, 1730, p. 119.

<sup>266</sup> Schwartz, C.G., De Genuinis Opii Effectibus in Corpore Humano, Praes. A.E. Büchner, Halae, 1748, p. 15 et seq.

eighteenth-century pharmacology was the effect a drug had upon the blood. The usual method of determining this was either to examine the blood at the post-mortem or to add the substance to the blood drawn from a vein. Alston, however, attempted to study its effects on the blood and circulation in a living animal.<sup>267</sup> For this he chose the frog, which was to become the most popular subject for later experiments with opium. Alston, assisted by a microscopist Robert Fullarton, administered a few drops of an aqueous solution of opium into the stomach of a frog by means of a small tube. The animal was then placed in a glass cylinder so that the experimenters were able to view through a microscope the blood vessels in the membranes of the hind foot. They saw no alteration in the colour or consistence of the blood, but noted a diminution of its velocity, even although there was no apparent change in the pulse frequency. They noted further that, as the frog recovered from the effects of the opium, the velocity of the blood gradually increased. This experiment was repeated several times with the same results, although it is not recorded that they were compared with control

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<sup>267</sup> Alston, C., Medical Essays and Observations,  
Edinburgh, 1742, 5, 153.

experiments on frogs not dosed with the drug.

In another experiment Alston studied the effects of directly injecting the opium solution into the veins. Shortly before, two students at Edinburgh had made this experiment injecting the solution into the vein of a dog, which had collapsed immediately with violent and fatal convulsions. Alston in repeating this work, with his colleague and fellow student at Leyden, Alexander Monro, primus (1697-1767), took precautions hitherto neglected in experiments of this type. They took half an ounce of opium and dissolved it in four fluid ounces of water. The solution, carefully filtered and warmed to blood-heat, was then injected very slowly into the crural vein of a dog. At first they injected ℥ xv with no observable effect, and so sixty minutes later they injected a further ℥ viii. Following this the dog was convulsed and its pulse small and frequent. When an hour later they injected a further ℥ ix, the pulse became slow and full and in one minute the dog died.<sup>268</sup>

In his last experiment Alston fed to a dog

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<sup>268</sup> Alston, C., Medical Essays and Observations,  
Edinburgh, 1742, 5, 156.

120 grains of crude opium mixed with its food. He records that there was a slow onset of symptoms, a paralysis developing and lasting several days, after which the dog made a slow recovery.<sup>269</sup> Now Alston knew that Mead had reported the administration of the same dose to a dog but dissolved in hot water and with immediate and fatal effects.<sup>270</sup> Unfortunately, Alston saw no significance in this and made no attempt to repeat his experiment or to explain the different results. This apparent 'lapse' may be explained by the fact that, although in his experiments the techniques and care displayed were a distinct improvement on previous studies, the experiments themselves were treated rather as curiosities and played a secondary role in the elaboration of his theories concerning the drug. They contributed nothing to his argument that opium acts directly on the nerves;<sup>271</sup> indeed, if he had taken them seriously, he might have suspected some action via the circulation after absorption.

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<sup>269</sup> Alston, C., Medical Essays and Observations,  
Edinburgh, 1742, 5, . 157.

<sup>270</sup> Mead, R., Essays on Poisons, London, 1702, p. 141.

<sup>271</sup> Alston, C., Medical Essays and Observations,  
1742, 5, 168 et seq.

b. The Whytt-Haller controversy concerning the action of opium.

Mid-way through the eighteenth century, experimental studies on opium were associated with the theories of sensation and irritability proposed by Robert Whytt and Albrech von Haller, who disagreed on the mode of action of the drug and, in particular, on the question of its specific effect upon the heart.

Robert Whytt (1714-1766) was Professor of the Institutes of Medicine in the University of Edinburgh. He had studied medicine in Edinburgh, London, Paris and Leyden and had graduated M.D. in Rheims in 1736. It was not long after his graduation that he became dissatisfied with the theories concerning the involuntary motions of the heart and lungs and in 1744 he began a study of this problem. His first treatise on the subject, Essay on the Vital and Other Involuntary Motions of Animals, was published at Edinburgh in 1751. This work, which introduced the modern concept of reflex action and has been described as one of the most remarkable in the history of neurology,<sup>272</sup> demonstrates the importance Whytt placed

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<sup>272</sup> Fulton, J.F., Readings in the History of Physiology, Springfield (Ill.), 1930, p. 242.



upon experiment. In the preface he records that the work is based on experiment and observations, to which he adds that only facts provide a sure foundation for doctrine.<sup>273</sup> His experiments include studies of the reaction of animals to stimuli after the extirpation of different parts of the nervous system and in one of them he discovered that destruction of the corpora quadrigemina abolished the reflex contraction of the pupil in response to light - a phenomenon that became known as Whytt's reflex. Whytt, as a result of his researches, discarded the Stahlian doctrine of the 'rational soul' as the cause of involuntary motion and substituted the idea that these movements were due to the effect of a stimulus acting upon an unconscious sentient principle. According to this theory, the continuous involuntary movement of the heart is due to the stimulation of the sentient powers by the returning venous blood.

The experiments with opium were made in the course of a study of the behaviour of the heart after its removal from the body. Whytt observed that, when the heart of a frog is removed, its contraction becomes progressively slower and weaker.<sup>274</sup> This he explained as

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<sup>273</sup> Whytt, R., Essay, Edinburgh, 1751, p. v.

<sup>274</sup> Ibid., p. 365.

being due to the absence of the stimulation of the venous blood and he held that the contractions of the isolated organ, owing to a residual sentient power of the fibres, must eventually cease unless some other stimulus is applied, e.g., <sup>it</sup>ir~~r~~itation with a needle. In the first experiment with opium, he injected an aqueous solution of the drug into the stomach of the frog via the mouth and, at the same time, injected the solution per anum.<sup>275</sup> In less than fifteen minutes the animal showed signs of paralysis and in half an hour it had lost all power of motion. Three hours after the injections the thorax was opened and Whytt reported that the heart was motionless and would not respond to any form of stimulation. He then removed the head and probed the spinal column without observing motion in any part of the body. The experiment was repeated<sup>276</sup> and the thorax opened one hour after the administration of the opium. In this animal the auricles were found to be distended with blood and the heart to be beating very slowly at the rate of one pulsation every  $3\frac{1}{2}$  seconds, which he compared with another experiment when he laid open the thorax of a

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<sup>275</sup> Whytt, R., Essay, Edinburgh, 1751, p. 370.

<sup>276</sup> Ibid., p. 372.

healthy frog and found the heart beating 64 to 66 times a minute.<sup>277</sup> A third experiment, using a smaller dose gave the same result.<sup>278</sup> In this case the heart, when cut from the body, increased its movements for a short time in response to irritation, but soon resumed its slow rate of pulsation. Whytt concluded that the effect of opium was to render all parts of the body insensible, including the heart, the motion of which ceased when it became insensible to the stimulus of the returning venous blood. It was, of course, a common observation that the heart beat for a time after other parts of the body became insensible and this phenomenon Whytt attributed to one of three possible reasons: (i) the fibres of the heart are endowed with a greater sensibility, (ii) its sensibility is not so easily destroyed as that of other parts by opium, or (iii) the organ is supplied with nerves from the cerebellum, which is less affected by the drug than those parts of the brain whence the nerves of the voluntary muscles are derived.

The prevailing opinion at this time was that the opium affected the nervous papillae of the stomach

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<sup>277</sup> Whytt, R., Essay, Edinburgh, 1751, p. 365.

<sup>278</sup> Ibid., p. 372;

<sup>279</sup> Ibid., pp. 373-4.

and through them the brain and nervous system. To demonstrate this Whytt made the following experiment. He took two frogs and removed the heart of each. After five minutes he injected a solution of opium into the stomach and cloaca of one of them. This animal made no further movements after half an hour and failed to respond to stimulation; the control animal on the other hand showed movements for a period of  $2\frac{1}{2}$  hours.<sup>280</sup> From this result Whytt argued that, since the heart had been removed, the opium could not have mixed with and been distributed by the blood, and, therefore, its effects must be due to direct action on the nerves at the site of application. We note, however, that only two experiments were performed and, although one was meant to be the control, there is no evidence that they were made together. Furthermore, the results were not entirely conclusive. In the drugged animal the full effects of opium do not appear to have taken place, for, when a probe was inserted into the spinal cord, some

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<sup>280</sup> .Whytt, R., Essay, Edinburgh, 1751, p. 375.

Note: The strength of the solution is not recorded in this work but was later given as  $\frac{1}{2}$  oz. of drug dissolved in 8 fl.ozs. of water. It was injected at a temperature of 60°F. (see Essays & Observations, Edinburgh, 1756, ii, 282).

contraction of the fore-legs was observed. These considerations are sufficient to indicate that Whytt drew far-reaching conclusions concerning the action of opium on very slender and inadequate experimental evidence.

At the same time as Whytt was preparing his Essay, the great Swiss physiologist, Albrecht von Haller (1708-1777), and his student, Johann Georg Zimmerman (1728-95), were making experiments on animals to study problems of sensibility and irritability.<sup>281</sup> On April 22 and May 6 1752, Haller read before the Royal Society of Science at Goettingen the two parts of his memoir "De Partibus Corporis Humani Sensilibus et Irritabilibus",<sup>282</sup> in which he expounded Glisson's principle of 'irritability' as an innate power of contraction. He declared that sensibility was possessed only by the nerves and tissues they served and that irritability was independent of all nervous influence. This was contrary to Whytt's theories, and after the publication of Haller's memoir the Scots physician

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<sup>281</sup> Zimmerman's thesis Dissertatio Physiologica de Irritabilitate was published in 1751. Between this date and the publication of his own memoir in 1752, Haller records further experiments on 190 animals.

<sup>282</sup> Haller, A. von, Comment.Soc.reg.Gottingae, (1752), 1753, 2, 114.

renewed his experiments in an attempt to demonstrate that all muscular action was under nervous control. This was the broad issue that gave rise to the subsequent controversy between the two men. An associated problem and one on which they also differed was the action of opium upon the animal body.

Haller had observed that opium destroyed the peristaltic motion of the intestines and the irritability of the body but, contrary to the supposed observations of Whytt, not the motion of the heart.<sup>283</sup> The effect of the drug on peristalsis had first been reported in 1745 by Abraham Kaau Boerhaave (1715-1758), a nephew of Herman Boerhaave. Kaau Boerhaave administered 3 grains of opium to a small dog and noted among its effects the cessation of peristalsis.<sup>284</sup> Similar observations were made by Haller and another of his students, Johann Adrian Sproegel (1728-1807), when, in 1750 and 1751, they were making an experimental study of the effects of poisonous substances (including corrosive sublimate, arsenic and

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<sup>283</sup> Haller, A. von, Comment.Soc.reg.Gottingae, (1752), 1753, 2, 117.

<sup>284</sup> Kaau Boerhaave, A., Impetum Faciens dictum Hippocrati per corpus consentiens Philologice et Physiologicè Illustratum Observationibus et Experimentis passim firmatum. Lugduni, 1745, p.401.

opium) on the movements of the stomach and intestines. They demonstrated that, when opium is given to a dog, peristalsis ceases with an apparent loss of irritability of stomach and intestines.<sup>285</sup> Most important, however, was Sproegel's observation that when 3 i (60 grs.) of crude opium is given to a dog, or 10 grains to a frog, the heart continued to beat after peristalsis had stopped.<sup>286</sup> Thus Haller was led to the belief that opium had no direct effect upon the irritability of the heart. Whytt's arguments to the contrary were dismissed as being based on a few experiments with dying animals.<sup>287</sup>

Whytt's reply to Haller's doctrine of irritability appeared in 1755 in an essay entitled "Observations on the Sensibility and Irritability of the Parts

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<sup>285</sup> Haller, A. von, Mémoires, Lausanne, 1756, vol.i, pp. 305, 306, 331, 333 (Expts. 368, 372, 444, 451).

Sproegel, J.A.T., Experimenta circa varia venena in vivis animalibus instituta, Gottingae, 1753, pp. 25, 31, (Expts. 15, 21).

<sup>286</sup> Sproegel, J.A.T., Ibid., pp. 25, 28, 30 (Expts. 15, 17, 21).

<sup>287</sup> Haller, A.von, Comment.Soc.reg.Gottingae (1752), 1753, 2, 157.

of Men and other Animals",<sup>288</sup> part of this work was devoted to their difference of opinion concerning the action of opium upon the heart.<sup>289</sup> This specific question, however, was taken up in greater detail in another paper which appeared in the same year under the title "An Account of Some Experiments made with Opium on living and dying Animals".<sup>290</sup> This paper, which was read before the Edinburgh Literary and Philosophical Society on 7 August, 1755, in both title and contents was a direct answer to Haller's criticism of the earlier work. The previous experiments were repeated and the results of twenty new experiments were put forward in support of the theory of nervous control of the muscles and of the action of opium and its direct effect upon the heart.

The first experiments were devoted to demonstrating that opium affects the heart to a greater extent than decapitation and destruction of the spinal cord. Opium was injected into the stomach and cloaca of frogs and the heart-beat compared with that of frogs that had

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<sup>288</sup> Whytt, R., Physiological Essays, Edinburgh, 1755, p.97.

<sup>289</sup> Ibid., p. 205 et seq.

<sup>290</sup> Whytt, R., Essays and Observations, Edinburgh, 1756, 2, 280.



been beheaded and pithed.<sup>291</sup> The results as recorded are summarized in Table VIII. Whytt treated the results as comparable without explaining why the heart-beat was counted only once in each of the first two experiments or why at different times in the others. The next series of experiments was designed to observe the effects upon the heart after the brain and cord had been destroyed. The head was removed from a frog and the spinal cord probed and the abdominal muscles and thorax exposed by removing the skin or, alternatively the abdomen was laid open. The trunk was then immersed in a solution of opium. After a period had elapsed it was removed, the thorax opened and the movements of the exposed heart observed. Comparative experiments were made by repeating the process on a frog with the brain and cord intact.<sup>292</sup> The recorded results of this work are summarized in Table IX. Because in frogs, when the brain and spinal cord were destroyed, the action of opium upon the heart appeared to be retarded, Whytt concluded that the drug must act chiefly through the central nervous system.<sup>293</sup>

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<sup>291</sup> Whytt, R., Essays and Observations, Edinburgh, 1756,  
2, 281-283.

<sup>292</sup> Ibid., pp. 285-292,      <sup>293</sup> Ibid., p. 303.

Table VIII. Results of experiments made by Whytt to compare the effects of opium to those produced by destroying the brain and spinal cord of a frog.

Essays and Observations, Edinburgh,  
1756, 2, 281-283.

Time (min) after in- jection of opium or destruct- ion of brain and cord	Heart-beats per minute (normal between 60-70)			
	Expt. 1 Opium in- jected via mouth and cloaca	Expt. 3 As for 1. using stronger solution of opium	Expt. 4 Frog beheaded cord des- troyed with a probe	Expt. 5 Frog beheaded cord des- troyed with red-hot wire
10	- *	-	45	-
16	-	-	40	-
30	-	-	36	-
35	-	-	-	30
50	-	-	30 (small and feeble)	-
60	17	-	-	-
1 hour 6	-	7	-	-
1 hour 51	-	-	-	20

\* The symbol - indicates that no result appears in the text for this time.

Table IX. Results of experiments performed by Whytt to observe the effect of opium on the heart after the brain and spinal cord had been destroyed. . Essays and Observations, Edinburgh, 1756, 2, 285-292.

Time in minutes after removal from solution of opium	Brain and Spinal Cord				
	Intact Expt. 6 Immersed 35 min.	Destroyed Expt. 7 Immersed 36 min.	Intact Expt. 8 Immersed 60 min.	Destroyed Expt. 9 Immersed 60 min.	Intact Expt. 10 Immersed 35 min.
0	6	26	9	8	9
6	- *	27	-	-	-
7	-	-	-	15	-
16	-	-	7	-	-
25	8	-	-	-	-
41	6	-	-	-	-
42	-	-	-	-	13
1 hr. 9	-	-	-	-	6
1 hr. 11	5	-	-	-	-
1 hr. 15	-	18	-	-	-
2 hrs. 0	-	16	-	-	-
2 hrs. 28	2	-	-	-	-

\* The symbol - indicates that no result is given in the text for this time.

Two further experiments were made to confirm this. The abdomen and thorax of frogs were opened and the heart observed while the body was immersed in a solution of opium. The heart of the whole animal ceased to beat after 20 minutes, that of the decollated and pithed frog after 33 minutes.<sup>294</sup> Whytt explained that, in the case of the latter animal, the opium could not act through the central nervous system so that its effects were not apparent until it has been absorbed and carried in the blood to affect the nerves of the heart by direct contact.<sup>295</sup>

Associated with these experiments were studies of the effect of opium on the isolated heart. Whytt made three control experiments, removing the hearts of frogs and immersing them in fountain-water heated to 60°F. These were followed by tests where hearts were immersed for different times in a solution of opium, using water from the same source and heated to the same temperature. He reported that, although after immersion for 10 minutes in water, the heart continued to beat about

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<sup>294</sup> Whytt, R., Essays and Observations, Edinburgh, 1756  
2, 291-2, 305.

<sup>295</sup> Ibid., pp. 303, 305.

twenty pulses a minute, it was motionless after immersion for the same time in opium solution. He gradually reduced the period of immersion in opium from 10 to 7 to 6 then to 5 minutes, and only in the latter case was he able to observe movement in the organ after removal from the opium solution.<sup>296</sup>

The last experiments recorded by Whytt were made by one Robert Ramsay, a student in Edinburgh, and were used to illustrate the speed with which opium acted. In his first experiment Ramsay injected a solution of opium into the rectum of a small dog. In less than a minute the dog was unable to stand on its hind legs and had lost the use of them inside 4 minutes. In the second experiment a solution containing 36 grains of the drug was injected through a wound in the abdominal cavity. It was reported that the animal lost the power of its hind legs almost instantaneously. Two minutes after injection the dog was convulsed and after four minutes it was senseless.<sup>297</sup>

The results of all these experiments confirmed

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<sup>296</sup> Whytt, R., Essays and Observations, Edinburgh, 1756, 2, . 293-6.

<sup>297</sup> Ibid., pp. 297-300.

Whytt in his opinions concerning the action of opium. He concluded<sup>298</sup> that the drug produced its effects by its action on the brain and spinal cord and that this was brought about by its direct effects upon the nerves at the site of application or, if absorbed, upon the nerves on the inner side of the heart and blood vessels. He attributed little significance, however, to the effects following absorption because of Ramsay's evidence that the drug has an instantaneous action, not, therefore, allowing time for any appreciable weight of the drug to enter the circulation. This was later to prove one of the most important arguments against absorption and transport in the blood. This immediate action also precludes the possibility of particles of the substance being mechanically transported along the nerves to the brain and cord. Whytt adopted the vague concept of 'sympathetic action' to explain the transmission of effects from the site of application to the sites of action:

".... Opium, by affecting the extremities of the nerves of the parts to which it is applied, does, by means of their connexion and sympathy with the

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298 Whytt, R., Essays and Observations, Edinburgh, 1756, 2, 301-314.

brain and spinal marrow, destroy or prevent, through the whole nervous system, the operation of that power upon which depend sensation and motion in the bodies of animals." 299

According to the theory of Whytt, a direct result of these effects is that the organs become insensible to the stimuli that excite them and it is from this cause that the animal eventually dies. It was logical for him to assume that opium must affect the heart, since he believed that the action of the drug was to render it insensible to the stimulus of the venous blood. To prove the heart not exempt from the action of opium was, therefore, essential to the support of the theory of the 'sentient principle'.

This new work failed to convince Haller who replied by attacking once again the manner in which Whytt had made his experiments and collected his evidence.<sup>300</sup> He did not believe it possible that the effects of opium could be studied using such extreme methods as opening the

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299 Whytt, R., Essays and Observations, Edinburgh, 1756, 2, 309.

300 Haller, A. von, Mémoires, Lausanne, 1760, vol. 4, pp. 125-131

abdomen, removing the head and destroying the spinal cord. He pointed out that from his experience a disembowelled animal died sooner or later without having been exposed to the action of opium and that under such conditions the effect on the heart might be attributed to a number of different causes. In the opinion of Haller, to determine with certainty the time of death by a study of the diminution of the pulse and to determine the exact difference in the pulse-rate between a whole and decapitated animal would require a greater number of experiments than Robert Whytt had performed. He repeated his earlier statement that opium destroys the peristaltic movement of the intestines but not the movement of the heart, and he pointed out that, should the heart stop beating, it retained its irritability and could be stimulated to movement. In drawing attention to his earlier statements Haller commented upon the obvious fact that Whytt had made no attempt to deny or confirm them by similar experiments of his own. The reason why the Scots physician failed to repeat the experiments of Haller and Sproegel is simply that he was, at the time, unaware of the exact nature of their work. Haller in his Memoir of 1752 to the Royal Society of Goettingen, does not give details of his own experiments or those of



Kaau Boerhaave or Sproegel. Whytt was, therefore, ignorant of the exact nature of the experimental work, a fact he indicated in his Physiological Essays in 1755 when, after saying that Haller had been deceived concerning the cardiac action of opium, he commented that one could not see how, since "he [Haller] had not told us in what manner his experiments were made".<sup>301</sup> In spite of this, one experiment at least in Whytt's report could have been used to contradict directly Haller's own observations. The experiment was one of those made by Ramsay. Here it was observed that when, after ten minutes, peristalsis had ceased, the heart was affected to the extent that it had been reduced from 150 beats per minute to 65 weak vibrations. But Haller strongly criticised the experiment and argued that the disturbance of the heart might well have been caused by the violent dissection of the ribs and could not, therefore, furnish proof of the action of opium. Furthermore, he was sceptical of the report that the initial rate of the heart was 150 pulses per minute, which he believed excessive.<sup>302</sup>

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<sup>301</sup> Whytt, R., Physiological Essays, Edinburgh, 1755, p.213.

<sup>302</sup> Haller, A. von, Mémoires, Lausanne, 1760, vol. 4, p. 126. Note. the resting heart rate of a dog is recognised to be 70-120 per min.

Thus Haller rejected Whytt's experiments and the objections raised against the theory of irritability. Haller's own experience had led him to the conclusion that opium destroys the sensibility of all parts of the body, but not the irritability of the heart, and it, therefore, follows contra Whytt that the irritability of that organ does not depend upon the sensibility. He disagreed also with Whytt's theory of the action of opium through the nerves and supported his arguments by reporting the experiments of the Italian scientist, Felice Fontana. Fontana in 1757 revealed that he had made some experiments using frogs to observe the effects of applying opium and alcohol to the exposed crural nerves.<sup>303</sup> He found that a solution of opium in alcohol (esprit de vin) affected the nerve, so that the muscle was not contracted when the nerve was irritated. When a simple aqueous solution of opium was used, however, the nerve appeared to be unaffected and the usual muscular contraction followed stimulation. He concluded that the effects in the first experiment must have been due to the alcohol. To investigate this possibility he exposed the crural nerves of both legs and applied alcohol to one of them.

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<sup>303</sup> Fontana, F., in Haller's Mémoires, 1760, vol. 3, p. 157.

He found that this nerve when irritated was incapable of causing any movement in the muscle, whereas stimulation of the other nerve produced a normal response.<sup>304</sup>

Fontana concluded that the opium itself does not act directly through its application to the nerves, but is possibly absorbed and carried in the arterial blood to affect the fibres and the 'gluten' of the muscle, the 'gluten' being the possible seat of irritability.

c. Experiments by Alexander Monroe with opium, camphor and alcohol.

Haller was not alone in criticizing the experimental studies of Whytt. Another critic was Alexander Monroe, secundus (1733-1817), the Professor of Physic and Anatomy in Edinburgh, who suggested that his colleague had been misled in the interpretation of one of the experiments. Whytt, when he removed the brain and spinal cord of a frog, found that the opium appeared to have a slower action than when these organs were intact (see Table IX), and he concluded that the drug must, therefore, act through the brain and cord. Monroe suggested an alternative explanation, which was that the destruction

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<sup>304</sup> Fontana, F., in Haller's Mémoires, 1760, vol. 3, pp. 210-12.

of the nervous system had affected the blood circulation so that the opium was not absorbed and carried to the organs of the body. These comments were included in a paper<sup>305</sup> *Monro* read to the Literary and Philosophical Society at Edinburgh in 1761, in which he described the experiments that he had made to investigate the role of absorption in the action of the drug. At the time this work was planned, the principal authors (with the exception of Haller whose reply to Whytt *Monro* had not read) all proposed that opium acted directly upon the nerves at the site of application and affected the rest of the body by sympathy. *Alston*, *Kaau Boerhaave* and Whytt all regarded effects following absorption as negligible. *Monro*, although he subscribed to the idea of action through the nerves, was not prepared to accept the suggestion that the effects of absorption were insignificant.

The reason for this appears to be that he had recently (1757) <sup>306</sup> suggested that the morbid matter of disease might be absorbed through the lymphatic vessels

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<sup>305</sup> *Monro, A., Essays and Observations*, Edinburgh, 1771, 3, 292 *et seq.* The comments on Whytt's experiment appear on pages 299-302.

<sup>306</sup> *Monro, A., De Venis Lymphaticis Valvulosis*, Berolini, 1757.

and carried in the blood. If this were true, it was not unreasonable to suppose that poisons and drugs could bring about some of their effects on the body in the same manner.

For his experiments Monro chose the frog and, as a preliminary measure, he recorded certain physiological observations relevant to the experiments he was to perform, i.e., the structure and movement of the heart, the effect on the heart of destroying the brain, and the effect on the hind limbs when (a) the circulation is stopped and (b) when the nerve supply is cut.<sup>307</sup> The experiments were designed to observe three things: first, the general effects of the drug when applied in different ways to the animal; second, its effects upon the nerves when applied to parts where the circulation had been stopped; and third, the part, if any, played by absorption. The last was achieved by applying the substance to parts of the body where the concomitant nerves had been divided.

The study of the effects of opium administered in different ways was the object of the first six experiments. To standardize procedure and to ensure the

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<sup>307</sup> Monro, A., Essays and Observations, Edinburgh, 1771,  
3, 295.

accuracy of results Monro used (a) a standard solution of opium ( 3 i of crude opium digested in one fluid ounce of cold water and filtered after 24 hours), (b) fully grown frogs and (c) experiments repeated two or three times, the mean result being recorded.<sup>308</sup> The methods of administration used were by mouth, on scraped linen to the limbs, injection into the cloaca and under the skin. He observed from these experiments that, when opium was given internally or applied to the skin, the effects were analogous to those of toxic doses in men and quadrupeds. In the first experiment he administered thirty drops by pouring it through a tube into the stomach. After four hours the frog was insensible, but it was noted that the flow of blood in the hind feet was not sensibly reduced. Monro does not record the manner in which he made this observation, but doubtless he used the technique of Alston. After ten hours the motion of the blood was considerably reduced and after 22 hours it had almost ceased. Twenty-six hours after the administration the animal showed no sign of life except that its heart continued to move feebly. In the second experiment, when

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<sup>308</sup> Monro, A., Essays and Observations, Edinburgh, 1771, 3, 303.

the drug was administered per anum, the animal showed no outward appearance of life after  $2\frac{1}{2}$  hours, although the heart continued to contract feebly at a rate of 18 times per minute, and this Monro compared to his earlier studies when he found that in a healthy full-grown frog the ventricle of the heart normally contracted 58 times per minute. In another experiment forty drops of the opium were injected under the skin of the leg and after 30 minutes the animal was completely paralyzed with the heart beating "22 regular, but feeble strokes in a minute". These results induced Monro to follow Whytt and oppose Haller on the question of the influence of opium on the heart. He suggested that Haller had been deceived into forming his opinion "by finding that the heart continued to move after the animal seemed to be dead in other respects by the action of opium."<sup>309</sup> It must be noted that, at this time, Monro had not read Haller's reply to Whytt, wherein he explained that, although the movements of the heart may be indirectly affected, opium does not itself affect its irritability.

After he had observed the general effects of

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<sup>309</sup> Monro, A., Essays and Observations, Edinburgh, 1771, 3, 321.

opium, Monro sought to discover whether the drug acted directly upon the nerves independently of the circulation. To do this he proposed stopping the circulation, either to the whole body by removing the heart, or only to one limb by ligaturing the vessel. The difficulty facing him was that, if the drug was administered in any of the ways previously tried, by the time it exerted its effects the animal would be dead or the nerves adversely affected by the absence of the circulation. Monro, therefore, sought a method of administration in which the effects of the drug would rapidly appear. He achieved this by dropping 30 drops of solution through a small hole in the cavity of the abdomen. The results of seven experiments indicated that by this mode of administration the heart-beat was reduced to half its normal value in two minutes and to about 20 beats after only four minutes. At the same time the limbs were extended with the muscles convulsed and, after a quarter of an hour, the animal showed no outward signs of life although the heart continued to beat feebly at 10 beats per minute for 5 to 6 hours. These experiments were repeated after stopping the circulation by cutting out the ventricle of the heart. The animal was affected in exactly the same way except that it took a little longer for the effects to be



achieved to the same degree.<sup>310</sup>   Monro was surprised to find that opium acted so quickly when administered this way, and he suggested that it must act by affecting the nerves of the peritoneum or the nerves of the bowels after passing through the peritoneum.   The increased time of action observed when the heart was cut out he attributed to the loss of the effects of absorption or alternatively to the dulling of the reaction of the nerves owing to the absence of blood.

To investigate further the action of opium upon the nerves, Monro cut across all the organs at the pelvis of a frog, leaving intact only the spinal nerves supplying the hind limbs.   To prevent the tearing or stretching of these nerves, he tacked the limbs to the trunk by means of thread.   Thirty drops of the solution were then injected under the skin of the hind legs.   After 15 minutes the hind limbs were motionless and insensible, but the forepart of the body was apparently unaffected after six hours.<sup>311</sup>   Monro reported that the animal "lived" until the following day, by which one assumes he meant that it

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<sup>310</sup>   Monro, A., Essays and Observations, Edinburgh,  
1771, 3,       317-319.

<sup>311</sup>   Ibid., p. 324.

continued sensible to stimulation and reacted by contraction of the muscles. In spite of the fact that Monro was prepared to recognize absorption as a contributory factor in the mode of action of opium, his interpretation of these effects was most definitely influenced by his conviction of action through the nerves. Instead of deducing that the fore-part of the body was protected from the opium because no circulation existed between it and the site of application (the later interpretation of Fontana), Monro suggested two other possibilities, both associated with the nerves, either (i) the nerves of the extremities do not bring the distant nerves to suffer by sympathy or (ii) the power of the nerves to convey impressions is lost when the circulation in the concomitant arteries is cut off. He argued further that, since the opium had acted upon the limbs in the absence of the circulation, it must necessarily have acted through the nerves. As a further illustration of this form of action, he exposed the sciatic nerve of a frog for the length of a quarter of an inch and poured upon it two drops of opium solution. The limb was unaffected.<sup>312</sup> Fontana, who made a similar experiment,

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<sup>312</sup> Monro, A., Essays and Observations, Edinburgh, 1771, 3, 325.

concluded from the result that the drug did not act through the nerves (see page 182).  Monro, however, who believed in this theory, found an alternative explanation and suggested that the substance must act on the tender extremities of the nerves and that through them it exerted its general effects.

The object of these last experiments appears to have been to confirm rather to discover the effects of opium on the nerves.  When this was achieved, Monro turned to study effects following absorption.  His first experiment was to study the effect of opium applied directly to the heart and vascular system.  He exposed the heart and injected the solution into a vein running along the "under middle part of the abdomen on the outer side of the peritoneum".  Twelve drops were injected into each of two frogs and six drops into two others.  He observed that, as soon as the solution entered the heart, it was rendered incapable of expelling its contents; and, "in much less than one minute thereafter, became so intirely paralytic, as not to make the least contraction on the strongest irritation, whether applied to its outer or inner part".<sup>313</sup>  In the next experiment he tied a ligature at the origin of the aorta and through an opening above the ligature poured the solution through

the arteries. The result was that all the muscles were convulsed in less than a minute.<sup>314</sup> From these results Monroe drew the most far-reaching conclusions to support his preconceived idea on the mode of action of the drug. He observed once again that the heart is not exempted from the action of opium, commenting that in these experiments the drug comes into contact with the inner side of the heart, "in which way it will be applied, if absorbed". When the solution was injected into the aorta, the arteries were empty and, because of this, he suggested that the opium could not have acted by mixing with and rarefying the blood. Instead, he decided it must have acted on the vessels themselves. The mechanism of this action is explained in the following passage:

"Of the different substances composing the sides of the larger arteries, we can suppose the nerves alone capable of suffering by the application of opium, so as to communicate that sufferance by sympathy; and therefore this experiment seems to furnish abundant proof, that the large arteries are provided with nerves distributed on their inner coat".<sup>315</sup>

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<sup>313</sup> Monroe, A., Essays and Observations, Edinburgh, 1771, 3, 330.

<sup>314</sup> Ibid., p. 331.

<sup>315</sup> Ibid., p. 333.

Thus Monro reconciled the fact of absorption with action through the nerves. These experiments had merely proved that opium injected into the circulation exerts its effects violently and with great rapidity than when administered in other ways. Monro, however, firmly believing in the action through the nerves, interpreted the results as supplying an abundant proof of the existence of those nerves on which his theories depended.

The last experiments were designed to show that opium absorbed into the vessels produced similar effects. The hind limbs were isolated from the trunk except for the venous and arterial vessels. About 100 drops of opium solution was applied on lint to the hind limbs of each of five frogs. The animals were convulsed after  $2\frac{1}{2}$  hours. It was found that the convulsions intervened after only  $1\frac{1}{2}$  hours when the solution was injected under the skin.<sup>316</sup> In another experiment the spine was cut across half-way along the body and the lower part of the cord destroyed by means of a red-hot wire. Twenty hours after this operation opium was applied to the skin of the hind limbs. Four hours after the application the frog suffered from severe convulsions.<sup>317</sup>

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<sup>316</sup> Monro, A., Essays and Observations, Edinburgh, 1771, 3, 335.

<sup>317</sup> Ibid., p. 336.

These results led Monro to the conclusion that the poison was absorbed into the circulation and carried in the blood to affect parts of the body at a distance from the site of application.

Monro suggested as a result of this work that opium acted in two ways:

(i) it affected the nerves to which it is primarily applied bringing the rest of the nervous system to sympathize,

(ii) it is absorbed, mixes with the blood and affects the nerves of the heart and blood vessels.

In effect both methods are the same, differing only in the location of the nerves affected. Nevertheless, although Monro restated the doctrines of Alston and Whytt, he also recognized that opium could be absorbed and carried in the blood to distant parts of the body and that the effects produced as a result of this were significant. In fact, he suggested that in medicine the effects observed in patients were largely due to the action of the drug on the nerves following absorption. He reached this conclusion after noting the time taken for the opium to act.

He defended his beliefs concerning absorption against two arguments. The first arose from the common

observation that when animals that had died from large doses of opium were dissected, it was found that the opium had lost but little of its weight, and that often none had passed from the stomach into the intestine where it would meet the absorbing vessels. The use of these facts as an argument against absorption was due, suggested Monro, to two erroneous beliefs, first that no absorption was possible from the stomach, and second that all parts of the opium were equally active. Monro suggested, however, that, even after the effects were clearly observed in the animal, it would not be surprising to find that only a small part of the total drug was absorbed, because "it seems very probable that its active part makes but a small share of its bulk",<sup>318</sup> a fair prediction of the existence of a highly active principle in the crude drug. The second argument was that it would be difficult to visualize how the minute quantity that appeared to have been absorbed after mixing with the mass of the blood would be strong enough to affect so violently the organs of the body. Monro made no attempt to answer this directly and indeed he could have no

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<sup>318</sup> Monro, A., Essays and Observations, Edinburgh, 1771, 3, 339.

idea of the activity of the opium constituents. Instead, he merely suggested that those who offer this objection "little better conceive how it affects those nerves to which it is primarily applied, or the others by sympathy" ! <sup>319</sup>

Monro performed a similar series of experiments with ardent spirits, a mixture of white wine and French brandy, and camphor. These substances he was able to detect by smell and taste in parts of the body distant from the site of application. In the experiments with spirits, the mixture was applied on linen to the hind legs of two frogs and kept there for one hour. The legs were then amputated, the trunk skinned and the stomach and bowels infused in water. He found that after a time the water tasted and smelt of the spirits.<sup>320</sup> A similar experiment was carried out with camphor, which was applied in a fine powder to the hind legs and left for one and a half hours. After amputating the legs and opening the abdomen, Monro detected a distinct smell of camphor. The flesh and bowels of the frog were cut into pieces and infused in alcohol and water. After a

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<sup>319</sup> Monro, A., Essays and Observations, Edinburgh, 1771, 3, 339.

<sup>320</sup> Ibid., p. 342.



time both liquids were found to taste and smell of the drug.<sup>321</sup> Monro anticipated those who would argue that the substances had been distributed from the site of administration through the 'pores' of the body by repeating the experiment in an animal in which the circulation had been destroyed by removing the heart. He showed that in these circumstances no odour of the camphor can be detected in the trunk after application to the hind limbs.<sup>322</sup>

Monro concluded that spirits and camphor acted in the same manner as opium, i.e. by a direct effect on the nerves at the site of administration and by absorption into the blood to affect the nerves of the vessels and the heart. He was unable to determine to which of these modes of action one must attribute the greatest effect, although he agreed that, when the substance is applied externally to the whole skin, the effects must obviously follow absorption into the blood. This theory of the modus operandi of medicines was applied, as one might expect, to the other drugs, although Monro did not altogether deny the possibility that there might

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<sup>321</sup> Monro, A., Essays and Observations, Edinburgh, 1771, 3, 352, 357.

<sup>322</sup> Ibid., p. 355.

be some alteration in the body fluids particularly in cases where the drug was given over a prolonged period.<sup>323</sup> In spite of this reservation, Monro was later to become a principal opponent of Fontana's theory that poisons acted directly on the blood after absorption.

In 1765 the American Samuel Bard, a pupil of Monro in Edinburgh, published a dissertation<sup>324</sup> in which he described simple experiments with opium, recording his pulse rate after self administration of the drug. Ten years later Carl Joseph Wirtensohn published a dissertation<sup>325</sup> describing experiments with opium on the isolated heart after the manner of Whytt. Except for these dissertations, both of them principally concerned with the effect of the drug on the human body, there does not appear to be any further experimental work on the drug before the publication of Fontana's work in 1781.<sup>326</sup>

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323 Monro, A., Essays and Observations, Edinburgh, 1771, 3, 362.

324 Bard, S., De Viribus Opii, Edinburgh, 1765.

325 Wirtensohn, C.J., Dissertation ... demonstrans Opium vires fibrarum cordis debilitare, et motum tamen sanguinis augere, Monasterii Wesphal., 1775.

326 In the years between the studies of Monro on opium and 1781 a number of works on opium appeared. The

(v) Felice Fontana. Experiments in pharmacology and toxicology, 1764-1781

The most extensive series of experiments performed in the eighteenth century to observe the effects of drugs and poisons on living animals was carried out by the Italian scientist Felice Fontana. His pharmacological and toxicological research, in extent and method, might be compared to Haller's experimental work in physiology, although it must be admitted the results did not further the subject to the same degree or lead to theories of the same significance.

The Abbate Felice Gaspar Ferdinand Fontana was born on April 15th 1730 at Pomarole near Rovereto in the Austrian Alps. At an early age he travelled to Italy with his brother Gregorio and there he studied literature

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majority were concerned with the therapeutic use of opium, in particular with its use in inflammatory conditions. The value of opium in inflammatory diseases was at that time a matter of controversy. In general its use was condemned in such cases although de Haen, Stoerk and Huxham were opposed to this opinion (see Remmert, R.B., De Opii Usu in morbis inflammatoriis, Edinburgh, 1774, and Medical & Philosophical Commentaries, Edinburgh, 1771, ii, 19 et seq.).

and natural science, first at Verona and then at Parma, Padua and Bologna. In 1765, after a period in Rome, he went to Pisa where he was installed in the chair of logic. From Pisa he moved to Florence and, at the invitation of the Grand Duke (afterwards Leopold II), took charge of the Museum of Physics and Natural History founded by the Accademia del Cimento. Except for visits abroad, which included journeys to London and Paris, Fontana spent the remainder of his life in Florence, devoting his time to the museum to which he added a vast collection of wax anatomical specimens. In the later part of his life he became involved in politics and in 1799 his sympathy with the French Republic led to his arrest by the Austrians. He was released from prison by the Napoleonic forces when they re-entered Florence after Marengo. The remaining years of his life were more peaceful and he died, in 1805 following a stroke. He was buried in Santa Croce near Galileo and Viviani.<sup>327</sup>

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<sup>327</sup> For general biography see:  
 Adami, C., Un Eroe Della Scienza Felice Fontana.  
Pomarolese, 1730-1805, 1930; Garrison, F.H.,  
Bull. New York Acad. Med., 1935, 2, 121;  
 Marchand & Hoff, J. Hist. Med., 1955, X, 197.

Fontana's scientific studies were both extensive and varied. His physiological researches included studies of irritability (vide infra), the papillary reflex<sup>328</sup> and blood cells.<sup>329</sup> In plant pathology and<sup>330</sup> physiology he contributed work on rust disease in cereals, the false ergot<sup>331</sup> and 'circulation' in plants.<sup>332</sup> Pneumatic chemistry attracted him for a time and he made a study of the absorption of gases by charcoal and developed a gasometric apparatus.<sup>333</sup> His chemical studies were adapted to physiology and he invented a breathing apparatus where the carbon dioxide was absorbed by lime-water.<sup>334</sup> Other scientific achievements

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<sup>328</sup> De moti del iride, Lucca, 1767.

<sup>329</sup> Nouve osservazione sopra il globetti rossi del sangue, Lucca, 1776.

<sup>330</sup> Observazione sopra la ruggine del grano, Lucca, 1767.

<sup>331</sup> Observations sur la Physique, sur L'Hist. Naturelle, et les Arts, 1776, 7, 42.

<sup>332</sup> Ibid., 1776, 7, 285.

<sup>333</sup> Descrizione e usu di alcuni stromenti per misurare la salubrita dell 'aria. Florence, 1775;  
Reserches physiques sur la nature de l'air nitreux et de l'air déphlogistique, Paris, 1776.

<sup>334</sup> see Foregger, R., Anesthesiology, 1956, 17, 514.

included the discovery of the lymph vessels in the crystalline lens, observations of the nerve sheaths, recognition of the cell nucleus and investigation of tape-worm cysts in the brain of the sheep.<sup>335</sup>

The volume of his work, the nature of his writings and the importance of some of his discoveries mark Fontana as a careful observer and an inventive and meticulous worker. He believed in the superiority of experiment over hypothesis and conjecture, which he roundly condemned in his contemporaries. In discussing this he commented:

"J'espere qu'on distinguera dans mon Ouvrage les expériences, des inductions, les observations, des conséquences".<sup>336</sup>

While Fontana affirmed the importance of experiment, his work in physiology, toxicology and pharmacology is distinguished by his ready recognition of the considerable possibility of error in experiments involving the study of the reactions of living animals. Because of this, he took care in his experimental

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<sup>335</sup> Marchand & Hoff, J.Hist.Med., 1955, X, 198.

<sup>336</sup> Fontana, F., Traité sur le Vénin de la Vipère, Florence, 1781, Vol. 2, p. 64.

work to ensure adequate controls against which to compare his results. Furthermore, he adopted the principle that to eliminate errors in observation the experiment must be repeated a great number of times and his study of the viper venom consisted of no less than 6000 experiments, involving 3000 vipers and 4000 animals of various species.

Fontana's early work in physiology was inspired by the work of Haller. His early experiments on irritability, supporting the Hallerian doctrines, were recorded in a letter written at Bologna to Urbain Tosetti and dated 23 May 1757. This letter, which described his early experiments with opium, was largely devoted to contradicting Professor Tommaso Laghi (1709-1764) on the question of the sensibility of certain parts of the animal body. Haller included a translation of this letter in his Mémoires<sup>337</sup> and in the preface to the second volume of that work, written in 1759, he described the Abbé Fontana as his "esteemed friend".<sup>338</sup> Fifteen years later Fontana dedicated his

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<sup>337</sup> Haller, A., Mémoires, Lausanne, 1760, Vol. 3,  
p. 158.

<sup>338</sup> Ibid., Vol. 2, Preface.

long delayed work on animal physiology<sup>339</sup> to Haller, whose work in physiology had awakened in him a desire to experiment and to investigate the "more hidden phenomena of animal physics".

Fontana undertook to investigate more fully Hallerian irritability and the first results appeared in 1767 when he published his De Irritabilitatis Legibus (Lucca). In that same year he published his first work on the pharmacology of viper venom.

a. Studies of the viper venom.

When Fontana began his study of the viper venom, the subject had been a matter for discussion and argument among physicians and naturalists for over a century. Since earliest times men had been fascinated by the serpent whose bite could bring sudden death to its victim, and the search for a successful antidote appears to have involved as much credulity and knavery as the quest for the Philosophers' Stone. In the hundred years before Fontana's work the greater part of the literature on the subject had been concerned with

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<sup>339</sup> Fontana, F., Ricerche Filosofiche sopra la Fisica Animale, Lucca, 1775.



antidotes, which included viper fat,<sup>340</sup> olive oil,<sup>341</sup> Eau de Luce (a preparation containing oil of amber, alcohol and ammonia),<sup>342</sup> and 'snake stones', these last were bodies of a spongy texture which, when applied to the bite were said to absorb the venom.<sup>343</sup>

The first serious scientific study of the viper bite was by Francesco Redi (1626-1697), who demonstrated that the poisonous nature of the bite was due to the injection of a yellowish oil-like venom stored in small

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<sup>340</sup> Mead, R., Essays on Poisons, London, 1702, p. 29

<sup>341</sup> Mortimer, C., Phil. Trans., 1736, 39, 313; Atwell, J., Ibid., 1736, 39, 394; Williams, S., Ibid., 1737, 40, 26; Dufay, Ibid., 1738, 40, 444; Geoffroy & Hunauld. Mém.Acad.R.Sci., 1737 (pub. 1740) p. 183.

<sup>342</sup> de Jussieu, Hist.Acad.R.Sci., 1747 (published 1752), 55; de Malesherbes, Ibid., 1766 (published 1769), p. 58.

<sup>343</sup> Birch, T., History, London, 1756, Vol. 4, pp. 39-44.

Note The snake stones used in these experiments were said to have been taken from the head of an East Indian serpent which the Portugese call Copra de Capelo. Mead, however, described snake stones as manufactured bodies made up of calcined bones and other matter

(Essay on Poisons, London, 1702, p. 47).

sacs in the mouth.<sup>344</sup> These reports involved Redi in controversy with those who held other views, in particular with the physician Moise Charas (1618-1698), who believed that only an enraged viper was poisonous, its fury converting the saliva and other fluids to venom.<sup>345</sup> As a result of this controversy, Redi made further experiments to confirm his earlier discoveries.<sup>346</sup> Later others were able to confirm his findings.<sup>347</sup> Redi's achievement was to demonstrate the anatomy of the viper, the nature of its venom and the mechanism of its injection.

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<sup>344</sup> Redi, F., Osservazioni intorno alle Vipere, Florence, 1664. Note: It would appear from a paper by Sir Theodore de Vaux (Phil.Trans., 1694, 18, 162) that Sir Theodore de Mayerne (1573-1655) was familiar with the mechanism of the serpent bite. He suggested that mountebanks, submitting themselves to the viper for 'entertainment' or in an effort to sell an antidote, would empty the venom sacs of the creature beforehand.

<sup>345</sup> Charas, M., Nouvelles expériences sur les vipères, Paris, 1669.

<sup>346</sup> Redi, F., Lettera sopra alcune opposizione fatte alle sue osservazioni intorno alle vipere, Florence, 1670.

<sup>347</sup> Mead, R., Essay on Poisons, London, 1702, p. 22.  
Platt, T., Phil.Trans., 1672, 7, 5060.

He was unable to go further and admitted his inability to decide on the manner in which the poison brought about the death of the victim after it had entered the body. Thus Fontana, by endeavouring to discover the mode of action of the injected venom, took up the problem at the point where the seventeenth-century physician had left it.

Fontana began his study of the viper at Bologna about 1764. It was continued at Pisa and the first results were published in Lucca in 1767 under the title Ricerche Fisiche Sopra il Veleno della Vipera. The first observations were concerned with the anatomy of the vipers head, and he was able to demonstrate that the venom emerged from a duct which traversed the fang of the snake - a fact which Redi had missed.<sup>348</sup> He then went on to study the action of the venom. At that time a number of theories had been proposed and it was disagreement among the principal authors on the merits and demerits of these that had attracted Fontana to this subject. The different explanations put forward to explain the manner in which the poison acted and caused death had been collected and recorded by Dominique Brogiani (1716- ? ), Professor of Anatomy in Pisa<sup>349</sup>,

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<sup>348</sup> Fontana, F., Ricerche ..., Lucca, 1767, p. 22.

and Fontana began his work by re-examining these explanations, sometimes referring to his experiments and giving his own opinions, at other times repeating the criticisms put forward by Brogiani.

It had been suggested that the poison was either an acid or alkaline corrosive. By simple chemical tests Fontana was able to show that it showed neither acid nor alkaline reactions,<sup>350</sup> but, since this did not completely rule out the possibility of corrosive action, he referred the action of the venom to the action of poisons in general. He distinguished two types of poisons: (a) corrosive poisons which are destructive to tissue by local corrosion and to which no animals are immune, (b) those poisons which do not affect all animals alike, e.g., narcotics.<sup>351</sup> Fontana from his own experiments had noticed that not all animals appeared to be effected by the venom or affected to the same degree. On this evidence he decided against the possibility of the poison being of a corrosive nature.

In 1702 Richard Mead put forward his "mechanical"

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<sup>349</sup> Brogiani, D., De Veneno Animantium Naturali et Acquisito Tractatus, Florence, 1752, p. 6.

<sup>350</sup> Fontana, F., Ricerche ..., Lucca, 1767, pp. 62-64.

<sup>351</sup> Ibid., p. 47.

theory to account for the action of the venom.<sup>352</sup> He suggested that the injected poison was composed of needle-like particles which pierced the blood corpuscles to release the enclosed fluid (in fact a mechanical analogy to haemolytic action). Later, however, Mead became dissatisfied with this explanation, after it had been demonstrated that a dog could be killed by a rattlesnake within a quarter of a minute.<sup>353</sup> This led him to doubt if such a rapid action could be explained by an effect upon the blood. In seeking an alternative explanation he decided that the particles must act upon the nerves, explaining that the subtle fluid or animal spirits flowing through the nerves would allow a faster transmission of effects.<sup>354</sup> The particles (the theory was extended to include all poisons) were said to wound the coat of the nerve and the effects were immediately transmitted.<sup>355</sup>

Fontana began to investigate these mechanical theories by the obvious method of looking for the

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<sup>352</sup> Mead, R., Essay on Poisons, London, 1702, pp. 13-15.

<sup>353</sup> Hall, Phil. Trans., 1727, 35, 309.

<sup>354</sup> Mead, R., Essay on Poisons, London (3rd edition), 1745 pp. xxxiv, xl, xli.

<sup>355</sup> Ibid., p. xxx.

particles. He failed to find them and suggested that the minute cracks and fissures observed in the dried venom were such as would suggest the presence of minute sharp particles or crystals.<sup>356</sup> He further drew attention to the fact that here the convulsions were attributed to a pricking or wounding of the nerves and pointed out that such symptoms were known to appear when no particulate matter is present, e.g., in cases of bleeding to death.<sup>357</sup> On these considerations Fontana rejected Mead's mechanical explanations. Similarly he rejected the suggestion that death was due either to coagulation of the blood, following injection of the venom, or to general inflammation.<sup>358</sup> He was highly contemptuous of Buffon's belief that the action of venom as well as that of other poisons was due to the microscopic *animaçules* commonly observed in vegetables and animal solutions and which he (Buffon) believed to be molécules organiques.<sup>359</sup>

Fontana based his own explanation upon observations of the symptoms of poisoning. Mead had done the

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<sup>356</sup> Fontana, F., Richerche ..., Lucca, 1767, p. 75

<sup>357</sup> Ibid., p. 116

<sup>358</sup> Ibid., p. 107; see also Brogiani, D., De veneno..., Florence, 1752, p. 6.

<sup>359</sup> Fontana, F., Richerche ..., Lucca, 1767, p. 123.

same; he had noted convulsions in the victims and had deduced an effect upon the nerves. Fontana observed a loss of muscular action and deduced a direct action upon the muscle. His earlier experiments with opium had suggested to him that it acted by destroying the irritability of the muscle. The weakness and torpidity of animals bitten by the viper suggested to him that the venom acted in the same manner.<sup>360</sup> To demonstrate this he took fifty frogs, some he allowed to be bitten by the vipers; and others he poisoned by means of an envenomed lancet. All the animals exhibited torpor, insensibility and loss of muscular action. Although the heart could be stimulated to movement, stimulation of the nerves did not bring about a muscular response.<sup>361</sup> He, therefore, concluded that the venom destroyed the irritability of the elementary fibres of the muscles and, since he had observed the experimental animals to putrify rapidly, he suggested that this destruction of irritability was due to a putrefactive principle (un principio di corruzione) in the venom.<sup>362</sup> There, for a time, Fontana rested content, believing that he could inquire no further into

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<sup>360</sup> Fontana, F., Ricerche ..., Lucca, 1767, pp. 127-8.

<sup>361</sup> Ibid., pp. 133-4.

<sup>362</sup> Ibid., pp. 137-9.

the nature of the putrefactive process.<sup>363</sup> So far he had done little to advance the knowledge of the action of the viper venom except to add another theory to a subject already overloaded with possible explanations.

When the Ricerche was published, Fontana intended to write a second work concerning the remedies for the viper bite, but the failure of all substances tested caused him to put the work on one side. In 1777, however, Balthasar-Georges Sage (1740-1824) published a pamphlet<sup>364</sup> on the value of the 'volatile alkali' (ammonia) as an antidote, and this contradicted Fontana's own findings on this substance. At that time Fontana was in Paris, where he had arrived in 1776 bringing with him additions and corrections for the long delayed French translation of the Ricerche. Sage's pamphlet induced him to renew his study of the viper and although the object was at first to investigate the

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<sup>363</sup> Fontana, F., Ricerche ..., Lucca, 1767, p. 157-8.

<sup>364</sup> Sage, B.S., Expériences propre a faire connoître que l'alkali volatil-fluor est le remède le plus efficace dans les asphyxies: avec des remarques sur les effets avantageux qu'il produit dans le morsure de vipère, dans le rage, la brûlure, l'apoplexie, etc., Paris, 1777.



volatile alkali as a remedy, it led to many experiments that went far beyond the original intention. The results of these new experiments were published in Florence in 1781 under the title Traité sur le Vénin de a Vipère sur les Poisons Americains sur le Laurier-cerise et sur quelques autres Poisons Végétaux. Part I of this work is a French translation of the Italian work of 1667 and Parts II, III and IV report the work carried out in Paris during 1777 and 1778. A Supplement to the treatise records work carried out while the book was in preparation for publication. As the title indicates, this two volume work includes also studies of the curare arrow-poison and the cherry-laurel poison (vide infra).

In the Traité Fontana gives a careful report of all his experiments and meticulously records all results and conclusions. This deliberate care appears to have derived from his realization of the importance of the carefully planned experiment and his pre-occupation with the possibility of error in biological experiments:

"I know I have been tedious. I might have been less so and clearer had I chosen the synthetic instead of the analytical method. I preferred the latter and I have presented my experiments in the order I made them. I have not feared to

disclose my errors and to show how often I have been obliged to begin again. The analytic method is not the shortest or the most favourable to the writer but it is the most certain, most luminous and the only one which leads immediately to a discovery .... When the methods which led to a discovery are seen, the merits of the work and the authors opinions can best be judged. It will be free of the mystery and reserve which abound in writings formed on the synthetic plan which lack these landmarks which have guided the way to a discovery." 365

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365 Fontana, F., Traité, Florence, 1781, Vol. ii, p.62.

'Je sais que j'ai été trop long. J'aurais pu être plus court, et peut être même plus clair, si j'eusse suivi la méthode synthétique, au lieu de l'analytique. J'ai préféré celle-ci. J'ai présenté mes expériences dans le même ordre que je les ai faites. Je n'ai pas craint de mettre en vûe mes erreurs mêmes, et de montrer combien de fois j'ai été obligé de retourner sur mes pas. La méthode analytique n'est certainement ni la plus courte, ni la plus favorable a l'écrivain; mais elle est la plus sûre, la plus lumineuse, la seule qui conduise directement a la découverte ..... En voyant les moyens qui ont conduit à la découverte, on jugeroit mieux du mérite de l'Ouvrage, et des opinions de

The progress of Fontana's experimental or "analytical" method was governed by three principles: one, to multiply the experiments; two, to vary the experiments, changing methods and species; and three, <sup>to</sup> attempting to discover the sources of error.<sup>366</sup>

The first experiments were designed to test the truth of Sage's claim about the effectiveness of volatile alkali as a remedy for the viper bite and they were carried out on twelve sparrows. Each was bitten in the leg by vipers, six were treated locally with the 'antidote' and the remainder were left untreated to act as controls. All but one of the subjects died. The experiment was repeated differently, the birds being bitten after they had been made to swallow the supposed protective. All the birds died and there was no difference in time of death between those medicated and the controls. From these results Fontana concluded that volatile alkali was ineffective.<sup>367</sup>

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l'auteur. On n'y trouveroit point ce mystère, et cette reserve qui regnant dans les ouvrages presentes avec la méthode synthetique, dans les quels manquent les traces qui ont guidé à la découverte.

<sup>366</sup> Ibid., vol. i, p. 102.

<sup>367</sup> Ibid., vol. i, p. 111.

Fontana was, however, careful to restrict this conclusion to the sparrow. He realized at this stage that there were two factors that argued against the conclusion being applied generally to all species including man. The first was that, assuming the quantity of venom to be the same at each bite, the larger the animal, the smaller the dose in relation to size. The second was related to the fact that a substance that appeared dangerous or poisonous in a small animal might prove to have remedial activity in a larger animal.<sup>368</sup> To resolve these doubts Fontana embarked upon a series of experiments involving a large number of different species. They included frogs, pigeons, fowls, guinea pigs, rabbits, cats and dogs.<sup>369</sup> In no case did he find volatile alkali to be effective. He was later to investigate other reputed cures and found them either useless (e.g. quinine bark, leeches, theriaca, viper fat, and olive oil)<sup>370</sup> or of only a limited application (e.g. ligature, lunar caustic<sup>371</sup>).

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<sup>368</sup> Fontana, F., Traité, Florence, 1781, vol. i, p. 111.

<sup>369</sup> Ibid., vol. i, pp. 112, 117, 120, 122, 125, 127, 128.

<sup>370</sup> Ibid., vol. ii, 7-13, 66.

<sup>371</sup> Ibid., vol. ii, pp. 22-29, 46-57, 310-324.

As the work progressed the investigation of cures became secondary to the study of the action of the venom itself. Fontana had observed that the time of onset of death was proportional to the size of the animal bitten and at the same time it appeared to be related to the size of the viper and to the time the fangs were inserted in the flesh. In order to reduce this last variation he adopted and improved the technique used in earlier studies of the viper<sup>372</sup> of decapitating the snake and manually inserting the fangs into the flesh. Fontana expressed the venom by compression of the poison sacs. Using this technique he could regulate the time of insertion of the teeth, choose the exact position of the bite, vary to some extent the volume of venom injected and, by keeping the teeth in place, prevent undue loss of poison from the wound. By the use of this method he was able to determine that the time of death for a sparrow was 6 to 8 minutes and for a pigeon 8 to 12 minutes.<sup>373</sup>

Another obvious factor concerned in the effects upon an animal is the number of times it is bitten, for,

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<sup>372</sup> See Phil. Trans., 1672, 7, 5062; 1736, 39, 399.

<sup>373</sup> Fontana, F., Traité, Florence, 1781, vol. i, 115.

it is this which determines the dose of venom injected. To demonstrate this Fontana submitted a number of different animals to the viper (pigeons, guinea pigs, rabbits, cats and dogs) allowing them to be bitten either once or twice or several times. In order to render the experiment comparative, each bite was delivered by a fresh viper and always in the same place. The results clearly indicated that the venom always produced a pathological condition and that its virulence increased with the number of times the animal was bitten.<sup>374</sup> This work not only demonstrated a dose-effect relationship for the venom, but also produced a possible explanation of Charas' theory that only an enraged viper could inflict a bite that caused death, its anger converting the saliva to venom. The observation that gave rise to this idea would appear to be that the enraged animal bites deeper and with greater force than one not so roused and thus a larger dose of venom is injected into the flesh.<sup>375</sup> To conclude his preliminary experiments Fontana experimented to observe the effects of the venom when injected into different tissues and organs of

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<sup>374</sup> Fontana, F., Traité, Florence, 1781, vol. i, 145.

<sup>375</sup> Ibid., vol. i, p. 133.

animals; skin, muscle, heart, brain, liver and so on.<sup>376</sup> It was an extensive series and the results together with the earlier observations led to the general conclusion that the venom was toxic to all warm-blooded animals and that its effects were influenced by the size of the animal, by the amount of venom injected, and by the part or organ bitten.

When these general facts had been established, Fontana attempted a more precise study of the pharmacodynamic action of the poison. His first task was to find the minimum dose of venom required to kill an animal. In order to do this, he had to find a method of separating small quantities of the venom and introducing it into the animal in such a way that none was lost in the operation. His first method, although ingenious and original, was unsatisfactory. He weighed four grains of venom, diluted it with double its weight of distilled water and painted the mixture over the surface of a piece of paper. The paper was then dried and cut into six equal parts. Each of these was bound to the exposed leg muscle of a sparrow. The results were, however,

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<sup>376</sup> Fontana, F., Traité, Florence, 1781, vol. i, pp. 147-9, 151-2, 164-5, 159, 164-5, 183.

too variable to be of any use.<sup>377</sup> We might ascribe the failure of this technique to a number of reasons, principal among them being non-uniform distribution over the surface of the paper and absorption into the paper affecting absorption into the wound. In his next attempt Fontana took three grains of venom which he laid on a piece of glass. He then took a piece of capillary tube, the end of which was shaped into the form of a scoop. This he plunged vertically ten times into the centre of the poison, wiping the scoop dry between each successive insertion. He reported the loss in weight of the venom to be 1/100 grain. He repeated the test several times, making tests to determine losses by evaporation, and although considerable variation in the result occurred, the overall result was sufficiently uniform for Fontana to decide that the loss in weight was approximately 1/100 grain and the scoop, therefore, removed 1/1000grain of venom.<sup>378</sup> He was now able to attempt to determine the dose necessary to kill an animal and from this information he hoped to arrive at some estimation of the toxic dose for man. Although it is

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<sup>377</sup> Fontana, F., Traité, Florence, 1781, vol. i, p. 228.

<sup>378</sup> Ibid., vol. i, p. 230.



obvious that Fontana took considerable care in this experiment, the results that he obtained must be viewed with some suspicion and the reported figure of 1/100 grain treated as being very approximate. There were two 'grain' weights in use in France at that time, one equivalent to 53 milligrammes and the other to 64 milligrammes. If one assumes that Fontana used the larger of the two, then he claimed to have weighed 0.6 milligramme which, on the evidence available, is outside the limits of accuracy for precision balances at that time.<sup>379</sup>

In order to determine the fatal dose of the venom, Fontana made an incision in the flesh and then plunged a scoopful of venom into the wound. The results are as follows:

#### Sparrows

One incision. - all died. Time 2-7 hours.  
(approx. 1/1000gr.)

Two incisions. - all died. Time 1-6 hours.  
(approx. 2/1000gr.)

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<sup>379</sup> The accuracy of precision balances available at the end of the 18th century is given as about one milligramme. Singer, Holmyard, Hall and Williams, (Editors), A History of Technology, Oxford, 1958, Vol. IV, p. 405.

Pigeons.

- |  |  |
|--|--|
| One incision<br>(approx. 1/1000 gr.)   | - majority of subjects survived. (precise details not given) |
| Two incisions<br>(approx. 2/1000 gr.)  | - 2 out of 12 subjects died.                                 |
| Four incisions<br>(approx. 4/1000 gr.) | - 9 out of 12 subjects died.                                 |

On the basis of these latter results and without further experiment Fontana took the figure of approximately 6/1000 grains as the fatal dose for a pigeon. Thus a sparrow weighing approximately 1 ounce is killed by 1/1000 grains of venom and a pigeon weighing about 6 ounces is killed by 6/1000 grains. Using these figures he deduced that the fatal dose for an ox (weight 750 pounds) is about 12 grains and for a man (weight 150 pounds) about  $2\frac{1}{2}$  grains. It is obvious that considerable approximations are involved in the handling of these figures. Of more significance, however, is the fact that Fontana, having accepted the validity of his animal experiments, now carried their comparative value to an extreme so that simple experiments on birds were applied directly to man. Fontana appears to have appreciated this and notes that in drawing these conclusions he had made three hypotheses concerning the

action of the poison:

- (i) the action is proportional to the dose of the venom,
- (ii) the action is proportional to the size of the animal, i.e., its power to resist increases with its size, and
- (iii) the effects on one species can be argued to be the same as on another.<sup>380</sup>

The recognition of these factors in relation to this experiment is of more importance to the history of experimental pharmacology than the experiment itself.

The next problem was the site of the action of the venom. Fontana had observed a reaction - 'une tache livide' - and a swelling in the area of the wound. This suggested that the action might be analogous to some local corrosive chemical action, although he had already cast some doubts on this theory. To investigate the matter he made vipers bite either the newly amputated limbs of pigeons or limbs connected to the body by no more than the thigh bone. In these cases the effects of swelling and inflammation did not develop

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<sup>380</sup> Fontana, F., Traité, Florence, 1781, vol. i, p.235.

and he abandoned the idea of local chemical or mechanical effects.<sup>381</sup> In spite of this, it still remained to be seen if death was the result of a local or a general effect. Fontana caused a number of pigeons to be bitten on the leg by a viper and he then amputated the limb after the local effects of inflammation and swelling had developed (having ascertained that amputation of the limb was not mortal to the birds). Of the twenty-four birds so treated all died within 3 to 20 minutes and he concluded that, since the source of local irritation had been removed, their death must have been due to a general effect of the venom on the body.<sup>382</sup>

During the course of the amputation experiments, Fontana made an interesting discovery. It was that the effects of the venom were not instantaneous. The fabled virulence of the viper suggested that the victim was instantly struck down and those who believed that its action was directly upon the nerves had no reason to doubt these reports. Fontana, however, found that there was a measurable interval of time between the bite and the appearance of the symptoms (an important factor in

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<sup>381</sup> Fontana, F., Traité, Florence, 1781, vol. i, p. 241.

<sup>382</sup> Ibid., p. 246.

explanations other than a direct action on the nerves at the site of the wound). The first experiment was to determine the time that elapsed between the bite and the appearance of the local symptoms, i.e., swelling and lividity. He amputated the legs of pigeons at regular intervals after the bite. Three series were carried out, amputating the leg (i) after 10 seconds, (ii) after 7 seconds and (iii) after 5 seconds. The results are summarized in Table X. The experiment was repeated, amputating the legs at 5 second intervals and observing the development of the general systemic effects on the bird. The results are summarized in Table XI. From the tables of results it can be seen that the local symptoms appeared after 15 to 20 seconds and that the amputation of the limb after this time did not protect the bird from the general effects of the poison.<sup>383</sup>

We note that in these experiments Fontana distinguished between local and general effects. In fact he treated them as two distinct conditions - "des deux maladies qu'occasionne la Vipère dans l'animal mordu". He had shown that the local 'disease' was not in itself fatal and he had formed the opinion that the

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<sup>383</sup> Fontana, F., Traité, Florence, 1781, vol. i, .  
pp. 248-50.

Table X. Results of Fontana's experiments with pigeons to determine the time that elapses between the viper bite and the symptoms of local reaction or 'disease'.  
Traité, Florence, 1781, Vol.i, p.242.

I	Time in seconds after viper bite										
	10	20	30	40	50	60	70	80	90	100	
Leg amputated at 10 second intervals	-	+	+	+	+	+	+	+	+	+	
II	7	14	21	28							
Leg amputated at 7 second intervals	-	-	+	+							
III	5	10	15	20	25	30					
Leg amputated at 5 second intervals	-	-	-	?	+	+					

(-) no symptoms developed.

(+) symptoms of local reaction.

Table XI. The results of Fontana's experiment to determine the minimum time for the development of general systemic effects following a viper bite in the leg of a pigeon.

Traité, Florence, 1781, Vol.i, p.248

Experiment	Interval between bite and amputation of the leg. (5 second intervals)	Effect on Pigeon
1	5	no effect
2	10	no effect
3	15	no effect
4	20	no effect
5	25	died in 10 hrs.
6	30	died in 3 hrs.
7	35	died 60 mins.
8	40	died 20 mins.
9	45	died 6 mins.
10	50	died 7 mins.
11	55	died 6 mins.
12	60	died 7 mins.

locally observed symptoms were not the direct result of the venom but due to a collection of 'morbific' matter driven to the site of the wound by the principe vital in order to relieve and protect the vital organs of the body. This humoralistic explanation served to explain why some animals survived the bite in spite of suffering from violent local reactions<sup>384</sup> and also why no local effects were observed in limbs amputated within 15 to 20 seconds of the bite (see Table X).

At this stage Fontana, who appears to have abandoned the idea of a putrefactive principle affecting irritability, turned to the investigation of alternative modes of action. He began by studying the action of the venom upon the blood, an obvious first choice, not only because direct action on the blood had been a common explanation of the action of poisons, but also because his work on opium had suggested the effects followed absorption. Furthermore, he had shown that snake venom exerted its effects after placing it in an open wound where it came into contact with blood. He began by mixing the venom with blood in vitro and because no changes were observed he concluded that the

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<sup>384</sup> Fontana, F., Traité, Florence, 1781, vol. i, p.254.



poison had no effect upon the blood. In spite of this it was decided to put the venom to the further test of direct injection into a vein and the injection experiment designed for this study indicates the care Fontana exercised to avoid errors due to accidental factors. His object was to investigate the direct action of the poison on the blood and, therefore, it must not come into contact with the tissues or with the cut sides of the vessel itself. To prevent this he carried out the following procedures. The jugular vein of a rabbit was exposed at the region of its bifurcation and two ligatures placed on one of the branches, one  $\frac{5}{6}$ " and the other  $\frac{1}{4}$ " from the main trunk (see Plate V). A syringe, fitted with a bend capillary tube  $\frac{5}{6}$ " in length, was filled with a solution of the venom from two vipers mixed with an equal volume of water. The further ligature was drawn tight and a small incision made in the vein between the two threads. The capillary tube of the syringe, after exclusion of air-bubbles, was then inserted into the vein and made to project about  $\frac{1}{3}$ " into the main trunk. The second

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<sup>385</sup> In the original work the distance is given as 10 lines, the line or ligne =  $\frac{1}{12}$  inch.

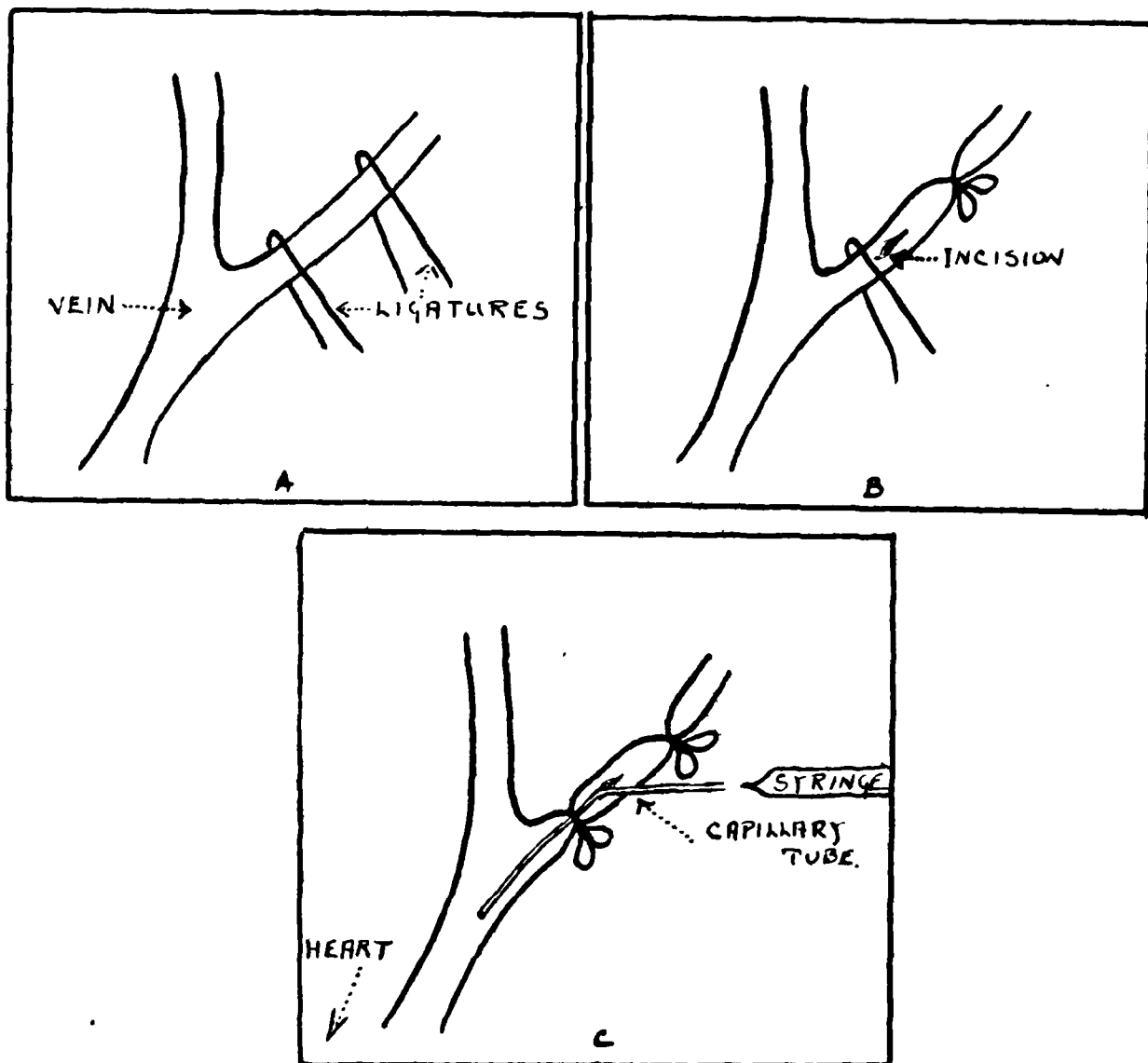


Plate V. Diagrams to illustrate the technique used by Fontana for injection into a vein.

ligature was tied so that the sides of the vessel were secured to the capillary tube, preventing the loss of venom by regurgitation and contact of poisoned blood with the cut vessel. After the venom was injected and blood drawn into the tube to ensure complete ejection of the poison, the syringe was removed and the ligature retied to prevent loss of blood. The first trials gave variable results but, after he had perfected the technique, Fontana obtained consistent results in a series of seven experiments. In each of these the effects were instantaneous; the rabbit was instantly convulsed and died in less than two minutes. Post-mortem examination revealed coagulated blood in the heart and larger vessels and some inflammation of the stomach and intestines.<sup>386</sup>

Fontana began this experiment without expecting to note any startling effects, since the venom had not appeared to affect the blood when mixed with it in vitro. He discovered, however, that in vivo the blood appeared to coagulate. Furthermore, the effects of the venom administered in this way were instantaneous and without that measurable period between injection and

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<sup>386</sup> Fontana, F., Traité, Florence, 1781, vol. 1, pp. 256-64.

effects which had been observed in the earlier work. Reviewing these unexpected results, he argued that, if the effects are different, then the circumstances must be likewise and he concluded that the differences in observed effects were attributable to the presence or absence of a 'living principle' in the blood. This principle, he suggested, is susceptible to the action of the poison and is so subtle that it is dissipated immediately the blood leaves the body, which explains why the venom has no effect upon extravasated blood or on newly amputated limbs. The action of the poison on this living principle results in the coagulation of the blood. This effect immediately kills the animal when the venom is injected near the heart, but if the animal is bitten in the leg, then some time must elapse before the coagulation develops to such a degree so as to be fatal. In this way Fontana explained the differences in his observations.<sup>387</sup>

This theory of a living principle in the blood was not new, Harvey had believed in such a principle and John Hunter had recently revived the theory that the blood was a living fluid.<sup>388</sup> Richard Fowler (1765-1863)

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<sup>387</sup> Fontana, F., Traité, Florence, 1781, vol. i, p.267.

observed:

"His [Fontana's] opinions respecting the existence of such a principle may be thought to receive no inconsiderable countenance, from the opinions of Harvey and of Mr. Hunter, concerning the life of the blood."<sup>389</sup>

Although the theory helped Fontana to resolve certain apparent contradictions in his experimental observations, he realized that it produced difficulties of its own. What, he asked himself, is the nature of this principle, where is it formed and how does it enter into the veins? To answer these questions further experiments must be made, but here was the greatest problem of all - where were these experiments to begin?

Unable to give a direct answer to this question, Fontana turned to a consideration of the action of the venom upon the nerves. One might ask, what were his reasons for this study? He had already explained the action of the venom by its direct effects upon the blood and had earlier rejected the nerves as the site of action

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<sup>388</sup> Hunter, J., Medical and Philosophical Commentaries, 1774, ii, 198.

<sup>389</sup> Fowler, R., Experimenta and observations on Animal Electricity, Edinburgh, 1793, p. 136.

for opium. His motives appear to be as follows: first, he was following his object of investigating the effects of the poison on all parts of the body; second, the symptoms of poisoning following a viper bite were of the kind commonly described at that time as being of nervous origin; and, finally, he conceived it possible that the nerves might be the source of the susceptible 'living principle' in the blood. A remark later in the work suggests that at this stage he was convinced that the nerves had some share in the effects of the venom.<sup>390</sup>

The first experiments consisted simply of applying the venom to the exposed spinal cord of decapitated frogs and comparing their response to stimulation against controls. The results indicated that, when the venom was applied in this way, it was effective. But this did not satisfy Fontana, who decided that with such small animals there was no guarantee that some of the poison had not diffused and penetrated other tissues and fluids.<sup>391</sup> He, therefore, devised a new technique for use with rabbits. He exposed the sciatic nerve and isolated it from the surrounding tissues by means of lead sheets between

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<sup>390</sup> Fontana, F., *Traité*, Florence, 1781, vol. II, p. 43.

<sup>391</sup> Ibid., Vol. I, pp. 269-273.

folds of linen. Using this preparation, he carried out an extensive series of experiments. Using the isolated poison fangs of the viper, he pierced the whole nerve, the divided nerve and the nerve to which a ligature had been applied. In all cases he compared the results with controls. In most cases the animals died, but not until some hours after the experiment and then without the characteristic symptoms of poisoning: in a number of instances death resembled the death observed in the controls, where the nerve was simply wounded with a needle.

From the results Fontana concluded that the venom was "innocent to the nerves".<sup>392</sup> Thus in spite of the 'nervous' symptoms of convulsions, unconsciousness, loss of irritability, the venom could not be shown to have any effect when directly applied to the nerve itself. There remained, however, the possibility that the nerves played an indirect part in the mode of action by secreting the 'living principle' which Fontana maintained was possibly the true site of action. The principal experiments to investigate this involved cutting-off the nerve supply to a limb before it was bitten by the viper. In the first experiments the sciatic and crural nerves of a

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<sup>392</sup> Fontana, F., Traité, Florence, 1781, Vol. I, p. 286.

rabbit were divided and later he added the precaution of incising the skin to divide the peripheral nerves. In three experiments the spinal cord was cut before the viper was allowed to bite the hind leg. In all cases the venom proved effective in spite of the neural isolation of the limb and the result confirmed Fontana in his opinion that the nerves played no part in the action of the poison.<sup>393</sup>

Fontana then turned to a cognate experiment and studied the effects when the circulation to the limb was obstructed. In the most important of these the arteries and veins supplying the leg of a rabbit were tied and cut below the ligature. After a period of some hours had elapsed, the subject was exposed to the bite of a viper. This experiment was repeated four times and in each case the local effects were reduced and the animal survived for a period of 3 to 11 hours after the bite. This Fontana accepted as further proof that the toxic effects of the venom were associated with the circulation.<sup>394</sup>

Fontana now returned to what appears to have

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<sup>393</sup> Fontana, F., Traité, Florence, 1781, Vol. I, p. 299.

<sup>394</sup> Ibid., p. 300.



been a major problem disturbing his mind. This was the difference in the observed effects of the poison upon the blood in vitro and in vivo. Obviously dissatisfied with earlier results, he repeated the earlier experiments, but this time he used controls. He took 20 drops of fowls' blood and mixed them with 3 drops of venom. The results were compared with 20 drops of the same blood used as controls. He discovered that the control coagulated in the usual manner, but that the venom sample became black in colour and remained fluid. Similar results were observed with the blood of the frog and the guinea pig.<sup>395</sup> Fontana now realized that it was the absence of coagulation that was significant. Hitherto he expected coagulation to be the obvious manifestation of the venom's effect upon blood. He was not the first to make this observation. In 1737 Geoffroi and Hunauld in a paper concerning the use of olive oil as a remedy for snake-bite had noted that the blood in the presence of the venom did not coagulate and further that there was an extravasation of serum into the tissues<sup>396</sup> It is certain that Fontana was aware of

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<sup>395</sup> Fontana, F., Traité, Florence, 1781, Vol. I,  
pp. 304-309.

<sup>396</sup> Geoffroi & Hunauld, Mém.Acad.R.Sci. 1737, (pub. 1740), pp. 183, 202.

this observation (it is recorded by Brogiani <sup>397</sup>) but, since it was but one of a number of conflicting reports, it is not surprising that he neglected it until his own studies provided confirmation.

These results convinced Fontana that the venom acted on the blood and in his final explanation of its mode of action he said that the venom was distributed to all parts of the body in the circulation; it coagulated the blood in the heart, lungs, liver and larger vessels, while dissolving the mass of blood in other parts. The serous part of the blood more fluid than before readily accumulated in the tissues round the site of the bite to produce the local symptoms. This partial coagulation and dissolution of the blood produces a violent derangement in the vital organs and a serious impediment to the circulation with the result that the animal dies.<sup>398</sup> In this explanation we note that both local and general effects arise from the same cause, and it is, therefore, more satisfactory than the earlier view in which the local effects were said to be due to the site attracting hypothetical "morbific humours".

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<sup>397</sup> Brogiani, D., De veneno animantium ....., Florence, 1752, p. 6.

<sup>398</sup> Fontana, F., Traité, Florence, 1781, Vol. I, pp. 318-9.

In an effort to look further into the haemotoxic action of the venom, Fontana attempted to observe the blood in direct contact with the venom. He mixed the poison with some blood of a frog and examined the corpuscles (les globules rouge) but failed to observe any effects that would explain the action of the venom in the body. After 8 hours there was no difference in appearance between the venomized blood and the control. After 8 days the poisoned blood was almost all dissolved but he argued the period was too long to explain the rapid effects of the venom.<sup>399</sup> In a further attempt to elucidate the action upon the blood he made a study of the nature of the venom. He had long regarded the venom as an animal gum and, since he believed gums to be rich in phlogiston (a substance said to give a black colour to the blood), he suggested that the action was due to the gummy principle in the poison. If this were true, however, other gums should affect blood in a similar manner. He subjected this argument to experiment observing the effect of gum arabic (gum acacia) on the blood. He found that the blood coagulated in the normal way. He, therefore, rejected the idea of a toxic gummy principle and

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<sup>399</sup> Fontana, F., Traité, Florence, 1781, Vol. I,  
pp. 308-9.

suggested instead that the venom was composed of a "principe gommeux, et une principe vénéneux destructif de la vie animal".<sup>400</sup>

In an extensive series of experiments, hampered by false starts and falser theories, Fontana eventually arrived at the conclusion that the venom was a haemotoxin. This discovery apart, his work on the viper venom was of considerable significance. First, the problem itself was extremely difficult and he had shown that it could be approached and studied experimentally. Surely few poisons could present such problems and dangers in their investigation! Second, Fontana had used carefully planned techniques and he had realized that certainty could be achieved only by making a large number of experiments with an equally large number of controls. Third, in the course of this work he took up, examined and, on the basis of experimental results, rejected a number of erroneous ideas concerning the action of the poison: they included mechanical effects of particles, chemical corrosion and action through the nerves. All of these were shown to be hypotheses based on superficial observations, although one cannot refrain from

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<sup>400</sup> Fontana, F., Traité, Florence, 1781, Vol. I,  
p. 311.

the comment that, as explanations, they were neither stranger nor less logical than the earlier ideas of Fontana himself. One of them, that of direction action through the nerves, continued to be accepted as the explanation of the action of poisons and drugs for some time after Fontana's publication. Finally, in this work Fontana emphasized the validity of relating the effects observed on experimental animals to man. He believed that, where the effects could be shown to be in proportion to the size and strength of the animal, they could, on that basis, be applied to man, and that it was both absurd and unlikely to suppose that substances, whose effects increased with dose and produced those effects in a wide range of species, would not act in the same way in man. These arguments resulted in one explanation for the many reputed cures of poisoning by the viper. On the basis of his experiments with animals Fontana calculated that, on a weight basis at least, two bites would be necessary to ensure, in most cases, the death of a full-grown man. He suggested that many of the so-called cures were due to a mistaken observation, the treated patient recovering, not because of the antidote, but because he had not received a fatal dose of the poison. Most certainly this would explain the report that a victim had recovered

after olive oil, a reputed antidote, had been applied  
an hour after the bite.<sup>401</sup>

b. Studies of ticunas arrow-poison.

In 1778, shortly after the completion of the viper experiments, Fontana moved to London where he stayed until 1779. There he met the anatomist William Cruikshank (1745-1800), whose work induced him to make a study of the regeneration of the nerves,<sup>402</sup> and William Heberden, whose gift of a sample of arrow-poison brought about a new series of pharmacological experiments. The work on snake venom, which had contradicted so many of the theories concerning the action of poisons, raised in Fontana's mind the problem of the action of other known toxic substances. He ventured to suggest that all animal poisons acted in the same manner as the venom, but he hesitated to extend this to vegetable substances.<sup>403</sup> We may surmise that on his arrival in London he had made up his mind to make experiments with some poison of vegetable origin and doubtless Heberden, learning of this, presented

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<sup>401</sup> Phil. Trans., 1736, 39, 394.

<sup>402</sup> Fontana, F., Traite, Florence, 1781, Vol. II, p.177.

<sup>403</sup> Ibid., Vol. II, p. 83.

to him the sample of curare. This consisted of a number of poisoned arrows together with a sample of the poison itself in an earthenware vessel in a tin case. With this material Fontana made a large number of experiments, using living animals, many of them being carried out in the presence of Jan Ingenhousz (1730-1799) and Tiberius Cavallo (1749-1809), with whom he was closely concerned at that time with the study of the absorption of fixed air by lime-water.<sup>404</sup> The results of the studies of curare were first published in 1780, in a paper written in Italian and communicated to the Royal Society by the linguist John Paradise.<sup>405</sup> An edited version was included a year later in the second volume of the Traité.<sup>406</sup>

It is not difficult to find reasons why Fontana was attracted to the study of the South American arrow-poison. It was a vegetable poison with a reputation for virulence equal to, if not greater than, the viper bite. Furthermore it had a number of features in common with the venom. Both acted through a wound

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<sup>404</sup> see Foregger, R., Anesthesiology, 1956, 17, 515.

<sup>405</sup> Fontana, F., Phil.Trans., 1780, 70, 163 (an English translation is given in an appendix to this volume).

<sup>406</sup> Fontana, F., Traité, Florence, 1781, Vol.II, p.83  
et seq.

in the flesh of the victim, both had a rapid and reputedly 'instantaneous' action and both gave rise to 'nervous' symptoms. Fontana admitted he was curious to see the analogy between the two poisons which were so active yet from such different origins<sup>407</sup> and this resulted in his following of the pattern of the venom experiments so that the action of the two substances could be compared and contrasted.

In the first experiments Fontana was very cautious in the handling of the poison, because of numerous reports that fumes from the substance were highly toxic. It had been commonly reported that, because of the danger from the fumes, its preparation was entrusted by the Indians to old women condemned to death.<sup>408</sup> Hérisant's work gave some results that appeared to confirm the story. He had decided to prepare the poison after the manner of the Indians, which was to dissolve it in water and then evaporate the solution to the consistency of a soft extract. In his first attempt he chose to carry out this process in a 'small closet'. After three

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<sup>407</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p. 88.

<sup>408</sup> For a history of this legend from the 16th century see McIntyre, A.R., Curare, Chicago, 1947, p. 6.



quarters of an hour, he noticed that a boy, whom he had left working in the closet, was sitting down and admitted to feeling sick and faint. Fortunately, fresh air and a cup of wine with sugar revived the boy and no after effects ensued. His curiosity aroused, Hérissant repeated the evaporation under the same conditions, this time staying in the closet himself. After an hour he became weak in his limbs and was forced to crawl into the open air where he was revived.<sup>409</sup> There is no reason to doubt the facts of this report. A man or boy in an enclosed space for an hour with a slow fire, probably of charcoal, would most certainly begin to feel faint and weak. It was unfortunate that Hérissant, persuaded by the stories he had heard, jumped to the conclusion that it was the fumes from the evaporating liquid that were poisonous and even more unfortunate that he made no experiments upon animals to prove the fact.

Fontana was more systematic. It was obvious to him that he must proceed with caution and so he began by forcing a pigeon to breathe the air issuing from the newly opened vessel, and then he made it inhale dust from the surface of the poison. He noted that the bird

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<sup>409</sup> Hérissant, F.D., Phil.Trans., 1751, 47, 77-79.

exhibited signs neither of poisoning nor of discomfort. He then collected in a large glass vessel fumes of the poison while it was being burnt on hot coals. A pigeon immersed in these fumes exhibited no signs of poisoning. The same results occurred when the bird was exposed to the fumes from an evaporating solution of the substance. No longer in doubt Fontana exposed himself to the fumes and in doing so disproved the many stories concerning the dangers attendant upon the preparation of the Indian poison.<sup>410</sup>

After a short chemical study of the poison, in which he discovered that it gives a dark colour with sulphuric acid (later to become a distinguishing test for certain of the constituent alkaloids), Fontana proceeded to investigate the action of the poison when given by mouth. It was generally accepted at this time that it was ineffective when given orally, because of reports that game killed by the arrows was safe to eat, although Brocklesby's single experiment with a bird had contradicted this opinion.<sup>411</sup> In the first experiment from 2

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<sup>410</sup> Fontana, F., Traité, Florence, 1781, Vol. II, pp.85-6.

<sup>411</sup> See p.~~10~~ above. Note; A similar experiment with the same result is reported in the J.Brittannique, 1754, 13, 85. This, however, is probably another report of Brocklesby's work.

to 6 grains were given to rabbits without apparent effect, so that Fontana concluded that the general opinion was correct. Nevertheless, he continued to experiment and, when he gave 6 grains dissolved in water to a young pigeon, the bird died in less than twenty minutes. He decided to repeat the earlier experiments and found that 8 grains given by mouth were fatal to rabbits and 5 grains to guinea-pigs. In the course of these experiments he observed that the same dose produced different effects in the animals and he attributed this to the state of the stomach at the time the poison was administered. In order to study this, three rabbits and two pigeons were kept without food before being given 3 grains of the poison. The results were compared with those of control animals which had been fed before the administration of the dose. He found that the fasting animals all died within 35 minutes, but of the controls only one died. Fontana's final conclusion on this matter was that the poison could be fatal when taken by mouth, but that a very large dose is required to kill even the smallest animal <sup>412</sup> (a modern estimate puts the fatal oral dose as 50 times that of the subcutaneous dose).

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<sup>412</sup> Fontana, F., Traité, Florence, 1781, Vol. II,  
pp. 89-91.

Fontana then turned to observing the effects when the arrow-poison was applied to a superficial wound in the skin. In the course of a number of experiments he observed the 'curarising' action of the drug: in one he scarified the skin of the thigh of a pigeon and applied the poison dissolved in water. After twenty-five minutes the bird was very weak and then entered into a state of "apparent death" for three hours, after which it recovered.<sup>413</sup> Later he drew attention to the relaxation and flaccidity of the body under the influence of the drug.<sup>414</sup> Fontana does not appear to have observed the symptoms of respiratory paralysis recorded by Hérissant but he did notice that the American poison, as he chose to call it, does not produce a local reaction at the site of injection. This was one of the differences that he was seeking between it and the venom.

The next step was to determine the fatal dose of the poison which, from his experience, he had reason to believe is very small. Whether it was lack of time or the absence of suitable apparatus that prevented him he did not attempt to measure the dose with the same

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<sup>413</sup> Fontana, Traité, Florence, 1781, Vol. II, p. 94.

<sup>414</sup> Ibid., p. 111.

accuracy observed in the case of the viper venom. On the contrary, the experiments as reported are crude. In one experiment he placed in the muscle "an atom of dry poison, scarcely perceptible to the eyes".<sup>415</sup> In this case, as in other instances where larger fragments were used, the animal did not appear to suffer, probably owing to the poison not dissolving in the wound. To assist the solution of the poison he adopted the technique of soaking small pieces of cotton in a solution of the substance, allowing them to dry and then inserting one into the muscle. Here, not for the first or last time in this work, Fontana is vague about his experimental method. In the first experiment he says:

"I steeped a very small piece of cotton in one fiftieth of a drop of the solution of the poison, containing such a proportion of water that the poison scarcely composed a fiftieth part." <sup>416</sup>

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<sup>415</sup> Un atôme de poison sec que je pouvois à peine appercevoir à la vûe simple (Ibid., Vol.II, p.95).

<sup>416</sup> Ibid., Vol. II, p. 94:

Je fis toucher un flocon à peine visible de cotton à un 1/50 de goutte de dissolution de poison dans une telle quantité d'eau, dont le poison pouvoit faire à peine le 1/50 partie.

This sample after drying was then laid into a wound in the muscle of a pigeon. The bird was not affected and so he repeated the experiment with about eight times the amount. This he found to kill a pigeon and a guinea pig and he concluded that above 1/100 grain dissolved is necessary to kill a small animal. It is difficult to see, from the facts given, how he arrived at the figure of 1/100 grain.

In another series of experiments, he demonstrated that the poison was more effective if injected directly into the muscles than if applied to the broken skin, and less effective if applied to parts where there is little or no blood supply, e.g., the ligaments and tendons.<sup>417</sup> He concluded from this that, when the poison is injected deeply and mixes with the blood and other body fluids, it is fatal and that the victim is beyond the aid of all remedies.<sup>418</sup> That deep penetration of the poison is inevitably fatal was not a startling discovery; doubtless the Indians knew that the arrow must penetrate deeply in order to bring down the quarry before it outran the hunter. What is of importance, however, is

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<sup>417</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p.96.

<sup>418</sup> Ibid., Vol. II, p. 102.

that Fontana related the effectiveness of the poison to the blood supply and so related the effects produced to the circulation.

This discovery was followed by an attempt to determine the time required for the poison to diffuse and exert its action on the body. The methods used were the same as those for comparable experiments with the viper venom: poisoned arrows were inserted into the thigh of young pigeons; in some ligatures were applied above the wound at predetermined intervals after the insertion of the poison; and in others the legs were amputated. Fontana found that, when the leg was amputated two minutes after injection, the animal survived, and that only two out of ten birds died when the leg was amputated after three minutes. Similar, although more irregular, results were obtained using rabbits and guinea-pigs.<sup>419</sup> It was, therefore, obvious that the action of the American arrow poison was not so rapid as the venom.

The many points of comparison with the venom induced Fontana to believe that this vegetable substance might possibly act in the same way. He, therefore, made similar experiments to see if it acted directly upon the

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<sup>419</sup> Fontana, F., Traité, Florence, 1781, Vol. II,  
pp. 102-104.

blood. He injected it directly into the jugular vein, using the same technique as that adopted for the injection of the venom. The animals died instantly.<sup>420</sup>

He mixed a solution of the poison with fresh blood and, when this did not appear to coagulate to the same degree as the control, he concluded that the poison must act directly upon the blood.

Fontana believed that in order to confirm this opinion it was necessary for him to demonstrate that the poison does not act directly through the nerves and again the experiments followed the pattern of the studies on venom. The sciatic nerve was exposed and isolated from the surrounding tissues, and the poison was applied directly in some cases to the whole nerve and in others to the wounded nerve and to the nerve after it had been severed. Although in many of the experiments the animal died, the period of time and the nature of death did not suggest that the poison was the immediate cause.<sup>421</sup> In the venom studies these results had been sufficient to prove the point that there was no direct action through

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<sup>420</sup> Fontana, F., Traité, Florence, 1781, Vol. II,  
p. 110.

<sup>421</sup> Ibid., p. 113.



the nerves. Similarly in this case, having shown that there was no direct action on the nerves, Fontana dismissed the nerves completely from a participation in the physiological events following the injection of the poison. Its action, he says, is all upon the blood.<sup>422</sup> He made little attempt to explain this action further and, although he did refer to the possibility of a susceptible living principle in the blood, he made but little effort to recommend it as an explanation saying:

" ..... all this is only mere conjecture, more or less probable, and unsupported by experiment. We ought to abide by sure facts, let the mode of explaining them be what it may."<sup>423</sup>

(italics mine)

It was shortly after he had written this that Fontana himself rejected, without experimental evidence, one reasonable argument contrary to his own theory. In all

<sup>422</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p.116.

<sup>423</sup> Ibid., Vol. II, p. 118:

"Mais ce ne sont la des simples conjectures plus ou moins probables, mais que l'expérience ne démontre pas. Il faut s'en tenir aux faits certains, quelle que soit le manière de les expliquer."

his experiments with poisons he had applied the substance directly to the body of the nerve. He realized, and knew that others would do likewise, that it was possible that the poison acted upon the extremities of the nerve and this would explain why, in his work, the poisons had not produced any effect. This argument, which Monro had used to explain the failure of his own experiments is reasonable, suggesting only that the extremities differed in some way either in anatomy or sensibility from the main body of the nerve. Fontana, however, dismissed it as mere hypothesis, as argument for the sake of argument. His reason for rejecting this, without recourse to the experimentation that he had so often advocated, was simply that the internal structure of the trunks of the nerves according to his observations did not appear different from that of the extremities and further that the trunk as well as the extremities is subject to pain.<sup>424</sup>

The theory of direct action on the blood in the case of viper venom followed from the experimental results. Fontana, however, was biased in his judgment when he put forward the same explanation for the action of the arrow-poison. He rightly called into question the

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<sup>424</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p. 119.

tendency among contemporary physicians to attribute all diseases and disorders to some condition of the nerves,<sup>425</sup> but he himself went to the other extreme and excluded the nerves altogether in the interpretation of his work.

In spite of these criticisms Fontana's London experiments were a valuable contribution to a knowledge of the arrow-poisons, and indeed the true value of his whole contribution to pharmacology and toxicology lies not in the theories that he formed but in the experiments that he made. This may be further illustrated by his last experiments with the arrow-poison, made on his return to Italy in 1780. The object of this new work was to observe the effects of the substance on snakes and land-turtles. He was, we know, interested in the action of the poison on different species and it is probable that this was the first opportunity he had of investigating these particular animals. In one of these experiments he used one of the arrows to pierce the foot of a land-turtle. In eight minutes the animal was unable to move and in fifteen it was apparently dead. He then opened the thorax and, although the heart was found to be motionless, it contracted when stimulated and,

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<sup>425</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p.162.

when freed from the membranes, continued to contract for several hours. The same results were observed in another turtle so that Fontana suggested that the arrow-poison affects the irritability of the muscles but not the irritability of the heart.<sup>426</sup>

c. Studies of solutions prepared from the Cherry-laurel leaves.

In 1779, still in London, Fontana began to study two other poisons of vegetable origin, oil of tobacco<sup>427</sup> and cherry-laurel water.<sup>428</sup> With the first he did little more than show that it was a violent poison when inserted into the pectoral muscles of pigeons; the second, however, became the subject of a more extensive series of experiments. Using the water obtained by distillation of the leaves, he discovered that two

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<sup>426</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p. 124.

<sup>427</sup> Fontana, F., Phil.Trans., 1780, 70, 209.

<sup>428</sup> The work on Cherry laurel is recorded in two memoirs. Both are published in the Traité, Vol. II, p. 125. The experiments in the first memoir were carried out in London and are also reported in the paper on the Ticunas poison (Phil.Trans., 1780, 70, 210).

teaspoonfuls (approximately 3 ii) killed a rabbit within seconds whether administered by mouth or per rectum.

But when the same quantity was applied to a wound in the muscles of a guinea-pig, three minutes elapsed before the animal was convulsed.<sup>429</sup> This result presented a problem to Fontana, for he believed that absorption through the open vessels of a wound would be faster than through the stomach or intestines. The slower action when applied to a wound confirmed his opinion that the poison cannot act directly through the nerves, but at the same time it contradicted his own explanation of a direct action on the blood. Following the pattern of the other studies, he applied the poison to the exposed sciatic nerve and found, as before, that the poison was ineffective.<sup>430</sup> When, however, he injected it directly into the jugular vein of a rabbit, he had another surprise, for, although he used doses up to one teaspoonful, the animal suffered no ill effects. It is difficult to explain why this should have been so and one can only suggest that, since these were the last experiments performed, the poisonous constituent, hydrocyanic acid,

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<sup>429</sup> Fontana, F., Traité, Florence, 1781, Vol. II, 127

<sup>430</sup> Ibid., Vol. II, 129.

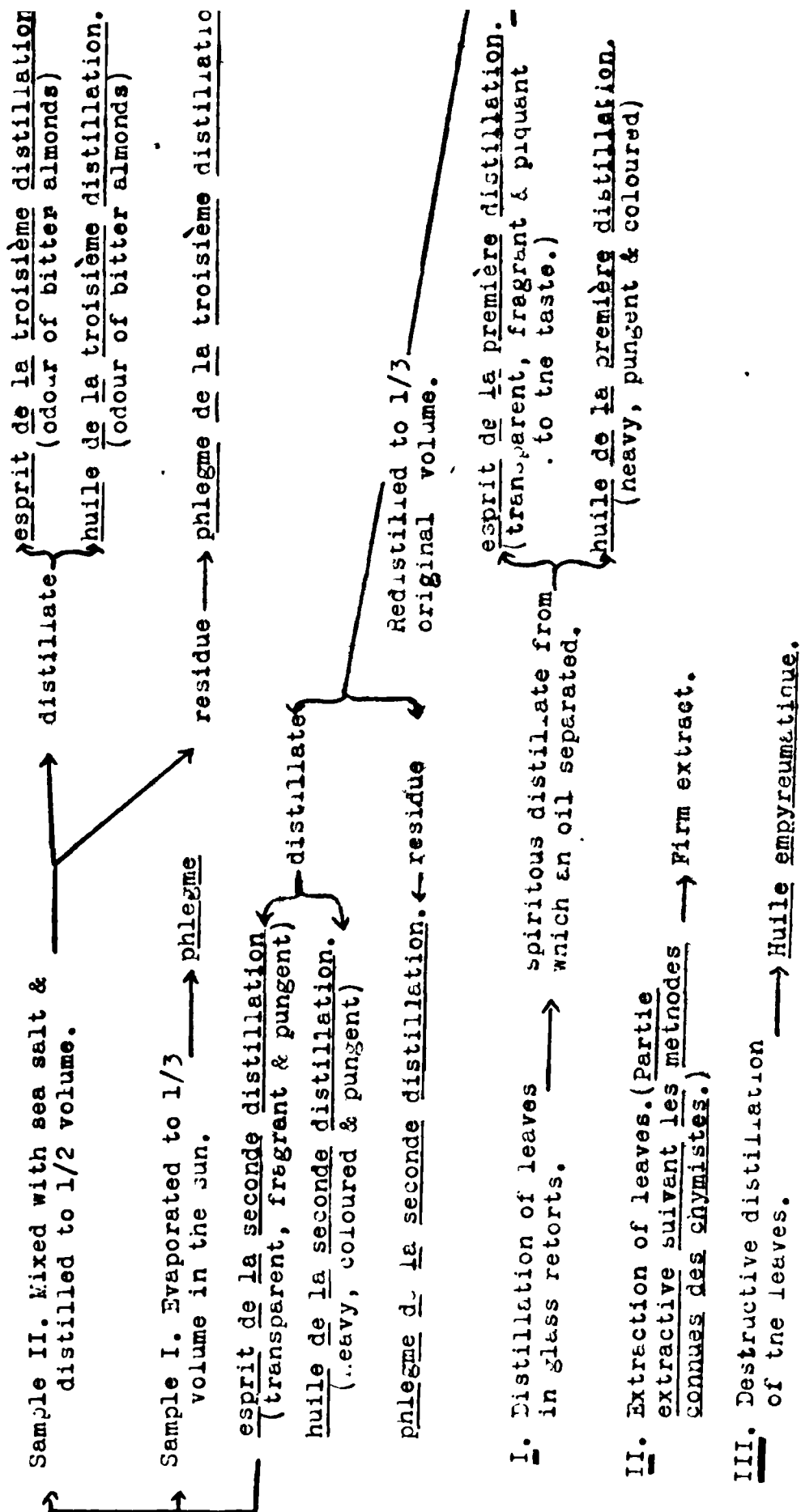
had volatilized from the sample. Although Fontana repeated the experiment, taking extreme care with his technique, he did not indicate that he ever used a fresh sample of the water.

Fontana accepted this result in spite of the difficulties it presented to his previous explanation and commented that all is confused, so confused in fact that he went so far as to ask if there were not some other way of destroying life without involving the blood and nerves. This was the final experiment of his researches in London and it was with some disappointment that he wrote at the end of his report to the Royal Society:

"When we think we have accomplished everything we suddenly find ourselves just where we began. Experiment is the only guide which we have to conduct us in our researches: experiment is indeed a secure way of avoiding error, but experiment does not always lead us to the more remote truths, nor always guide us to the secret arcana of nature, nor yet always conduct us wither we have proposed to go." 431

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431 Fontana, F., Phil.Trans., 1780, 70, 219. The translation is the official translation appended to volume 70 of the Phil.Trans.



Sceme to illustrate Fontana's preparations of the leaves of cherry-laurel. The titles underlined are those used by Fontana in the text to distinguish the distillates and oils.

He consoled himself with the fact of having shown that yet another poison does not act directly through the nerves and also with the prospect of making new experiments using more concentrated samples.

When he returned to Italy, his first object was, therefore, to attempt to separate or concentrate the toxic principle in the leaves. The processes he used are shown here in schematic form. Fontana administered each of these preparations to animals to observe their effects and of the 139 experiments recorded, 70 involved pigeons, 44 guinea-pigs, 19 rabbits and the remainder frogs and turtles.<sup>432</sup> Either the animals were made to swallow the preparation or it was placed in the mouth or into a wound. He found the extract and the empyreumatic oil to be harmless, and no doubt the processes of volatilization and decomposition of the hydrocyanic acid were the cause of this result. On the other hand, he reported that all the oils and distilled spirits were toxic, the doses varying with the preparation. Fontana singled out two results for discussion. The first confirmed earlier experiments and showed that preparations of cherry-laurel applied to wounds required a larger dose to produce rapid toxic

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<sup>432</sup> Fontana, F., Traité, Florence, 1781, Vol. II,  
p. 140 et seq.



effects than when the preparation was given by mouth. The second was that the preparation applied to the inner side of the mouth without touching the oesophagus or being carried into the stomach was capable of killing the animal in a very short time. The latter is an interesting observation giving evidence of buccal absorption, but unfortunately a careful study of the experiments as recorded indicates they do not fully justify the conclusion reached. The technique used involved wetting a piece of linen with the preparation and inserting it into the mouth or beak of the animal, which was held open to prevent swallowing or compression of the linen. All the pigeons so treated died of convulsions, but the guinea-pigs submitted to this operation remained unaffected.<sup>433</sup> Fontana, although drawing the conclusion given above, did not attempt to explain why some of his animals were free from the effects of the poison.

Again with these experiments Fontana had to admit they had proved somewhat of a disappointment. The poison did not appear to act in the manner of the other materials that he had tested in his studies and, since all fractions had shown toxicity, he had failed to

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<sup>433</sup> Fontana, F., Traité, Florence, 1781, Vol. II,  
pp. 145, 151.

isolate the poisonous principle from the leaves.<sup>434</sup>

He did not, however, give up the problem and continued to experiment while the Traité was in the press. Some of these new experiments were in his view satisfactory, with the result that he included a report of them in a supplement at the end of the second volume. It appears that, shortly after his experiments with the distilled fractions, his attention was drawn to two preparations then on sale in Italy for the purpose of culinary flavouring: the first was an oil described as essence of bitter almonds, and the second, which was prepared from this, went under the names of liquor of bitter almonds and liquor of peach flowers. Fontana discovered that the essence was in fact obtained from the leaves of cherry-laurel and, when he procured a sample, he began a new series of experiments with the object of proving the substance to be too dangerous for free sale to the public. He began by observing the effects upon vipers and other snakes<sup>435</sup> and, if this appears somewhat academic in view of the object of the work, it should be borne in mind that at that time substances destructive to cold-blooded

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<sup>434</sup> Fontana, T., Traité, Florence, 1781, Vol. II, p.157.

<sup>435</sup> Ibid., Vol. II, p. 328 et seq.

venomous animals were recognized as poisons par excellence. This is illustrated in the report Fontana made on these experiments: "J'ai vu, en général, que l'huile de Laurier-cerise est un poison très-puissant, même pour les Viperes ...." (*italics mine*).<sup>436</sup> A further illustration of this occurs in the work on opium (vide infra), when importance is attached to studies of the action of the drug on cold blooded animals, whose life was of longer duration and more tenacious.<sup>437</sup>

The experiments on snakes were followed by a number of others, in which the oil was applied to the eyes of pigeons and to artificial wounds made in the muscles. In all cases the animals died. Because of the problems associated with the mode of action of cherry-laurel preparations, he made a new series of experiments where he applied the substance to the brain and to other nervous tissues of the frog. He found that he was unable to stimulate any form of movement in the animal by irritating the nerves or brain tissues which had been in contact with the oil, although stimulation of other parts of the nervous system was

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<sup>436</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p.329.

<sup>437</sup> Ibid., p. 345.

effective. He concluded that the oil has some local effect on the nerves analogous to corrosion, but that this could not be communicated to the general nervous system.<sup>438</sup> So far, however, these results had done little more than to reaffirm that cherry-laurel preparations were poisonous and one suspects that it was not this but the results of the final experiments that induced Fontana to report this work in a special supplement to the Traité. In these he injected the oil directly into the jugular vein of a rabbit after the manner used in previous studies. He discovered that seven drops killed the animal instantly and he obtained the same result when he reduced the dose to five drops. No doubt surprised, he was tempted to repeat the experiment which failed in London and he injected a preparation distilled from the leaves. He found on this occasion that all the animals so treated died within a few seconds.<sup>439</sup> For him this result proved that cherry-laurel preparations, like the venom and curare, acted directly upon the blood, provided that a sufficient dose was given and that the preparation had been concentrated

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<sup>438</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p. 336.

<sup>439</sup> Ibid., Vol. II, p. 337 et seq.

by redistillation.

There is not much in this work that calls for favourable comment and it justifies the opinion that it was little more than a series of inconclusive and contradictory experiments.<sup>440</sup> As with the other studies, it was extensive and many experiments were conducted, but no new techniques were introduced and no original observations made. In fact, very few observations were made concerning the specific effects of the cherry-laurel preparations. The simple truth appears to be that in this study Fontana was less interested in the mode of action of the cherry-laurel itself than in confirming his own theory of the action of poisons on the blood. When eventually he succeeded in killing an animal by injection of the distillate, he demonstrated in his opinion, not merely the action of this particular poison but also that of all poisons. The problem that appears to have guided his work was not the elucidation of the mode of action of cherry laurel but that his first experiments had not, to use his own words, "conducted us wither we have proposed to go".

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<sup>440</sup> Woodville & Hooker, Medical Botany, 1832, Vol. 3,  
p. 517.

d. Studies of opium.

If Fontana's work on opium is of more interest than that on cherry laurel, it is because he was less concerned in it with his own theories than with the theories of others. His belief, that a poison or drug cannot produce its general effects upon the body simply by being applied directly to a nerve, had its origin in his early studies of irritability and sensibility. He confirmed this in the experiments that he made with alcoholic and aqueous solutions of opium and which Haller used to support his own doctrines.<sup>441</sup> These experiments, however, were few in number, and not long after their publication Monro had published his work which supported action through the nerves. Fontana was opposed to any theory that involved a direct action upon the nerves, whether at the site of administration or after absorption and, at the end of the *Traité*, where he discussed the role of the nerves in disease, he indicated his intention of taking up the subject of opium again when time permitted.<sup>442</sup> Apparently the opportunity occurred during the period 1780-81, when the final preparations

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<sup>441</sup> See p.182 above.

<sup>442</sup> Fontana, F., *Traité*, Florence, 1781, Vol.II, p.174.

for the publication of his treatise were being made. The experiments reported below all appear to have been carried out during this period and were completed in time for the results to be included under the title Sur l'Opium in a supplement to the second volume of the work.<sup>443</sup> They were all concerned with the two controversial questions associated with opium: first, its action upon the heart, and second, its effect upon the nerves at the site of administration.

In the study of the effects upon the heart, the first experiments were made upon the turtle. The organ was exposed by stripping off the pericardium and various solutions were directly applied. As in the earlier experiments with opium, he compared the action of alcoholic solutions of the drug with aqueous solutions, using spirit of wine as a control. He exposed the hearts of three turtles; to the first he applied plain spirit, to the second opium in alcoholic solution, and to the third the aqueous solution. He found that the heart of the third animal continued to beat for  $1\frac{1}{2}$  hours after the others had stopped. When he repeated the experiment he found, however, that the control, to which

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<sup>443</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p. 342 et seq.

spirit of wine had been applied, continued to beat after the others.<sup>444</sup> Similar contradictory results were observed when the experiment was repeated on frogs.<sup>445</sup> Reviewing these results, he suggested a weakness in the technique, observing that it was possible that the solutions were absorbed by the vessels of the thorax and carried to other susceptible organs. He turned, therefore, to the technique of Whytt, observing the effects upon the isolated heart. The results of the first experiments are shown in Table XII. From the results he concluded that solution of opium has no immediate effect upon the heart of the turtle, but again when he repeated the experiment on frogs, the results were too diverse and inconsistent to enable him to reach a firm conclusion. It was at this stage in his experimental work that Fontana turned to observe the effects of opium when directly applied to the nerves; and, when he eventually returned to the question of its effect upon the heart, his report is both vague and confused. He had resolved the problem into (a) the effect upon the actual movement of the heart and (b) the effect upon the force of the

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<sup>444</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p. 348.

<sup>445</sup> Ibid., p. 352.



Table XII. Results of experiments to demonstrate the effects of solutions of opium upon the newly isolated heart of the turtle.

Ref. Fontana, F., Traité, Florence, 1781, Vol. II, p. 350.

Solution	Results
Spirit of Wine	Motion of heart ceased in a few minutes.
Solution of Opium in Spirit of Wine	Contractions almost ceased after 15 minutes. Unable to stimulate the organ after 26 minutes.
Aqueous solution of Opium	Continued to move after 30 minutes but 'not forcibly'. After 2 hours 'all at rest'.
Water	Heart retained some motion after 2 hours.

heart:

"I wished to see whether opium when swallowed would diminish the force and velocity of the contraction of the heart, since it appears to have no action on this muscle, that relates to the duration of its motions." 446

Unfortunately, Fontana does not indicate which experiments in particular led to this latter conclusion; the experiments already cited were contradictory, and the only other experiments carried out in which he admits to observing the heart were those in which he studied the effects of destroying the spinal cord upon the action of opium. Furthermore, although he claimed to have conducted over a hundred experiments to discover the effect of opium upon the force and contraction of the heart, he gives no precise details of the experiments. He says only that the work with frogs gave results too variable

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446 Fontana, F., Traité, Florence, 1781, Vol. II, p. 368:

"J'ai voulu rechercher si l'opium donné par le haut ne diminueroit pas le vélocité et la force de contraction du coeur puisqu'il paroît ne rein faire sur ce muscle, relativement à la durée de ses mouvements."

to enable a conclusion to be reached and that in warm-blooded animals small doses appeared to increase the force and motion of the heart and large doses to decrease it. Fontana's experiments on this problem cannot be said to have contributed to its solution. They did confirm that the total effects of opium on the body were not solely attributable to its effects upon the heart, but the question of whether its action upon that organ were direct or indirect remained unanswered.

One series of experiments showed more positive results. This involved large numbers of frogs and guinea-pigs and demonstrated that both alcoholic and aqueous solutions of opium were poisonous, whether administered by mouth, injection into the cloaca, under the skin or directly to the brain or medulla oblongata.<sup>447</sup> Having confirmed this, the inevitable question arose: in what way does the drug act, directly upon the nerves or through the medium of the blood and circulation? Fontana, having in mind the results of his experiments with other poisons, believed that when swallowed the active particles of the poisons must be absorbed through the passages of the mouth, oesophagus, stomach and

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<sup>447</sup> Fontana, F., Traité, Florence, 1781, Vol. II, pp. 343, 351, 353.

intestines before the characteristic effects are observed. Monro, of course, also believed in an absorption of the poison or drug, but the two men disagreed upon the vital point of the action upon the nerves. Monro believed that direct action was possible; Fontana, on the basis of his experiments, thought the idea untenable. Fontana decided to put the matter to a further test by observing the effects when a solution of opium was directly applied to the nerve, and he arranged to study the effect upon the muscle when the drug was applied to the nerve of a nerve-muscle preparation. In this work the drug was to be applied only to the nerve and not allowed to come into contact with blood vessel or muscle. To eliminate errors the results were to be compared with a control and the experiment repeated a sufficient number of times to eliminate the accidental result arising from an imperfect preparation.<sup>448</sup> The whole experiment involved the careful dissection of over three hundred frogs and illustrates the scale on which Fontana was prepared to work. The method was as follows:-

He opened the belly of the frog, exposed the nerves which supply the hind legs (nerfs cruraux) and

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<sup>448</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p. 358.

freed them from all other parts. He then cut the vertebrae and body "à l'endroit précis ou l'on voit sortir ces nerfs" - at the precise point from which the nerves emerge; one presumes this 'precise' point to be one that cuts across the 7th, 8th and 9th spinal nerves. By gently agitating the neighbouring parts, the freed nerves were made to fall between the thighs of the animal. The thigh bones were then removed and the nerves isolated from all integuments for a distance of 8 - 10 lines (about 3/4 to 1 inch). The bared nerves, now freed from each other, were then laid in shallow glass vessels. Into one of these a solution of opium was placed to cover as much of the nerve as possible, into the other water to moisten the nerve which acted as the control (see Plate VI). The object of the experiment was to observe the effect of the drug upon the nerves by observing and comparing the reactions of the muscles on each side of the body after stimulation of concomitant nerves. Three hundred frogs prepared in the manner described were divided into ten groups of thirty. In the first group the nerves were immersed in the opium for 10 minutes, in the second group for 20 minutes, in the third for 30 minutes and so on to 100 minutes. The results obtained are summarized in Table XIII. Fontana

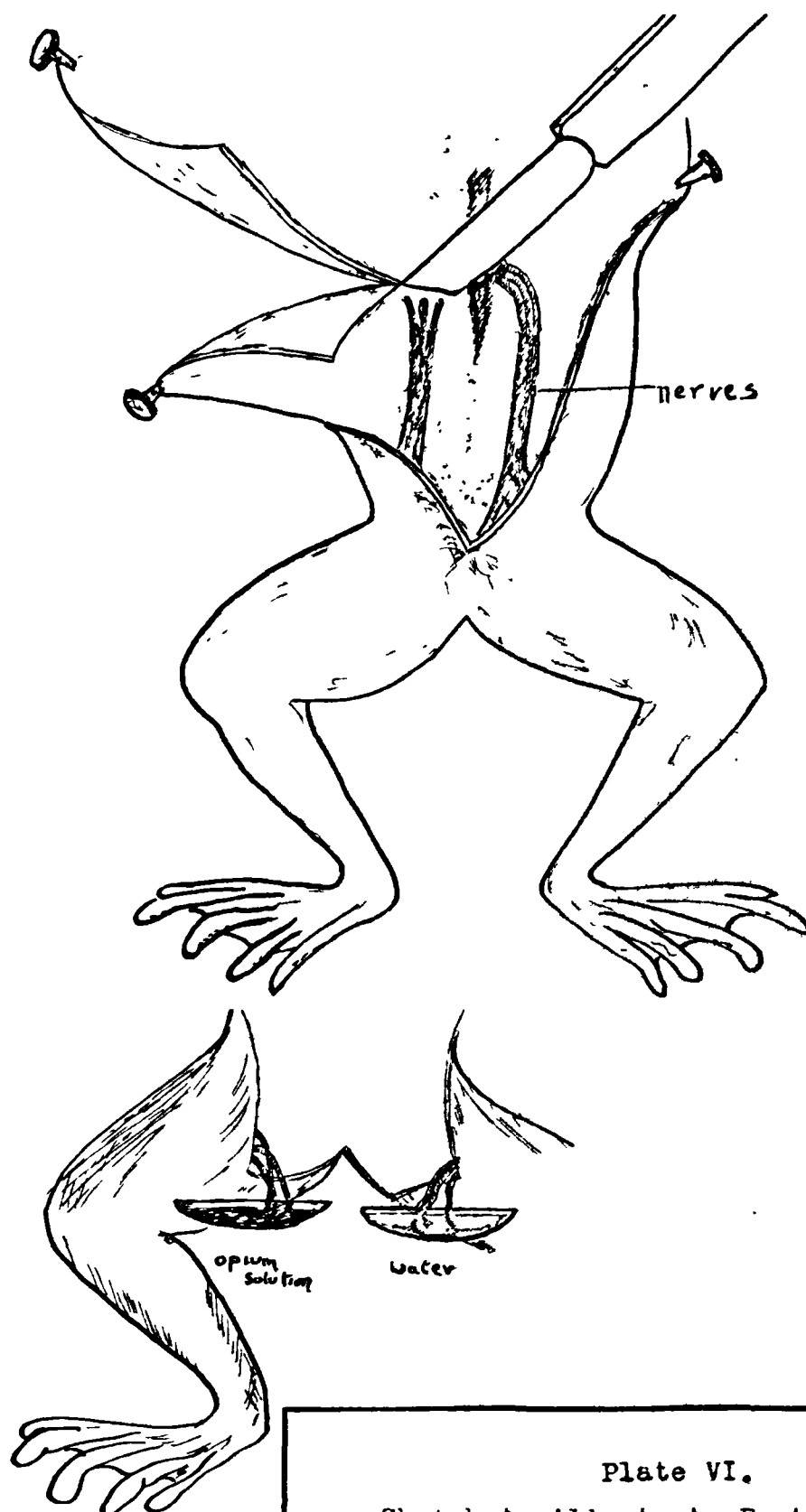


Plate VI.

Sketch to illustrate Fontana's experiment of immersing the nerves of a frog in a solution of opium.

Table XIII. Results of experiments to observe effects of opium when applied directly to the exposed crural nerves of a frog.

Ref. Fontana, F., Traité, Florence, 1781, Vol. II, pp. 358-9.

Time (in minutes) of exposure of nerve in opium solution	Reaction of feet and muscles on both sides of the body after stim- ulation of the nerves supplying the legs. (Nerves on one side immersed in opium, those on other side immersed in water and act as control - see Fig.VII)
10	Both feet contracted with an equal force
20	Equal contraction of both feet with a force similar to above.
30	Equal contraction of both feet, force of contraction diminished.
40	Feet barely contracted but muscles seen to contract and with an equal force on both sides.
50	Contraction of muscles feeble but equal on both sides.
60 70 80 90	Muscle contraction very feeble but no difference between one side and the other.
100	No contraction observed on either side of the body.

concluded after a study of these results that opium has no effect when applied directly to the nerves without coming into contact with other tissues.

Fontana found that, when the opium was directly injected into the jugular vein, it was immediately fatal,<sup>449</sup> and this fact together with the extensive studies on the nerves led him to conclude:

"opium does not act immediately upon the nerves, but has need of the circulation of the humours, in exerting itself upon animals." <sup>450</sup>

This, his final conclusion, might appear reasonable since it does not exclude an ultimate effect upon the nerves and brain after the process of absorption. Such an interpretation, however, is not tenable in the light of Fontana's own thoughts on the action of drugs and poisons. By similar experiments with other poisons he had reached the conclusion that, if a substance does not act directly upon the nerves, then it must act directly upon the blood

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<sup>449</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p.361.

<sup>450</sup> Ibid., p. 370. "Que l'opium n'agit pas immédiatement sur les nerfs; mais qu'il a besoin de la circulation des humeurs, pour exercer son action sur les animaux."



and when discussing his investigations on opium he says:

"my aim is to prove ..... the immediate action of opium on the blood, independent of the nerves". <sup>451</sup>

This he did not prove at all and his assumption that opium acts upon the blood was as unsupported by experimental evidence as the alternative and opposing theory of its direct action upon the nerves.

In summing up the toxicological and pharmacological work of Fontana, one might say that his theories of the mode of action of drugs and poisons are of less interest than the actual experiments that he made and the techniques that he devised to observe the action of substances when applied to different parts of the animal body. Most important was his recognition of the very real dangers of observational and experimental error in work of this kind. He knew that one could not form a correct opinion upon the results of a small number of experiments; such experiments, he emphasized,

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<sup>451</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p.363:  
"mon intention est de prouver l'action immédiate de l'opium sur le sang, indépendamment des nerfs."

must be carefully controlled and repeated many times to ensure certainty. To emphasize this, his treatise is grossly enlarged and rendered cumbersome by the faithful record of the false trails that he followed and the experiments that deceived him. Indeed, he had been deceived too often for him to believe that the work was finished and that there was nothing to add or complete but although prepared for opposition he insisted that any would-be opponent must adopt his standards for experimental procedure. He stated specifically that he would not acknowledge himself to be in error or feel in any way obliged to repeat his work on account of a few isolated experiments put up in opposition.<sup>452</sup> It would appear to be a somewhat arrogant and uncompromising attitude and yet not unreasonable from one who could claim to have made over six thousand animal experiments and who lived at a time when elaborate theories were compounded from the most slender experimental evidence.

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<sup>452</sup> Fontana, F., Traité, Florence, 1781, Vol. II,  
p. 370.

(vi) Experiments with Opium, 1782-1800

Fontana's theory concerning the action of drugs and poisons was not acceptable to the majority of physicians concerned with this problem, and work carried out in the two decades following publication of the Traité indicates that Whytt and Monro's explanation of action through the nerves was predominant.

In 1786, John Leigh, an American student in Edinburgh, published An Experimental Enquiry into the Problem of Opium (Edinburgh), a disputation which had gained for him the Harveian prize for 1785. In this work Leigh reported experiments in which he had extracted resins and gums from crude opium and tested them by administration to men and dogs. He discovered, as Neumann had reported many years before, that the resinous extract is highly active. He also made experiments to compare the action of opium given by mouth and by injection into the rectum, vagina and urethra. Attempts to introduce opium through the skin by applying an opium poultice proved unsuccessful.<sup>453</sup> The principal object

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<sup>453</sup> Leigh, J., Experimental Enquiry . . ., Edinburgh, 1786, pp. 94, 100, 102.

Note: It is interesting to note in connexion with the attempt to introduce opium through the skin that in 1797 an Italian physician Vincenzo Chiarugi

of this work, however, was not to investigate the mode of action but to improve the efficiency of the drug when used in practice. Leigh entertained no doubts but that opium exerted its effects through the nerves.<sup>454</sup> A survey of the experimental work of Whytt, Haller and Fontana was published in 1789 by Georg Christoph Siebold<sup>455</sup> (1765-98), who also recorded some experiments of his own on dogs and frogs in which he made simple observations on the pulse, respiration and body temperature after the administration of opium. A year later active opposition to the theory of Fontana appeared in the work of William Alexander of Halifax.<sup>456</sup> He too made a number of exper-

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(1759-1820) claimed success in the percutaneous absorption of the drug when he reported that powdered opium mixed with an ointment when rubbed into the skin calmed and brought sleep to a number of inmates in the Hospital of St. Boniface (an asylum) in Florence. Refs. Chiarugi, V., Nuovo metodo di somministrare l'opio esternamente per frizioni.

Florence, 1797.

see also Duncan's Annals of Medicine, 1798, iii, 194.

454 Leigh, J., Experimental Enquiry ..., Edinburgh, 1786, pp. 104, 119.

455 Siebold, G.C., Commentatio de Effectibus Opii in corpus Animale sanum maxime respectu habito ad eius analogiam cum vino, Gottingae, 1789.

456 Alexander, W., De partibus corporis animalis quae viribus Opii parent, Edinburgh, 1790.

ments and repeated some of the work of Whytt and Monro. One of his experiments opposed the theory of Fontana. He first carried out Fontana's own experiment and injected 33 drops of opium solution into the jugular vein of a rabbit. In this experiment, as expected, the animal died immediately, but, when the same dose was injected into the crural veins of each leg of another rabbit the animal only became sleepy and stupid and sustained no permanent injury. Alexander argued from this that the opium could not, therefore, act upon the blood alone, for, if it did, then the same effects would occur when injected into any of the larger veins. Alexander, himself, believed it to act directly upon the nerves and he opposed not only Fontana but also Monro, who believed in the possibility of a preliminary absorption.

In 1792 Monro returned to this subject in the course of some experiments associated with Galvani's theory of 'animal electricity'.<sup>457</sup> The results of the

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<sup>457</sup> In 1791 Luigi Galvani (1737-98), Professor of Anatomy in Bologna published the results of his experiments on electrical stimulation of the muscle (De viribus electricitatis in motu musculari, published in De Bononiensi Scientiarum et Artium Instituto atque Academia Commentarii, 1791, vii, 363-418). Galvani had observed that, when an arc composed of two

experiments were communicated in two papers to the Royal Society and published in book form in 1793.<sup>458</sup> In this

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different metals was placed, one end in contact with a nerve the other with the surface of the muscle, a contraction of the muscle took place. He conceived the opinion that the phenomena was proof of the existence of 'animal electricity', which flowed from the brain through the nerves to the muscles, which acted as a Leyden jar. This work caused a minor sensation and many physiologists and physicians in Europe repeated the experiments: Volta and Valli in Italy, Cavallo and Lind in England, Fowler and Monro in Scotland, Humboldt in France. As a result of further experiments, first Volta<sup>and</sup> then Monro expressed doubts concerning animal electricity, believing the reactions to be due to simple electrical phenomena. In a letter written in 1794, Volta reported that the effect came from a current originating in the contact of two dissimilar metals. For 'animal electricity' he substituted 'metallic electricity'. In actual fact Galvani's first observations were of phenomena which could be attributed to both these sources of electrical energy, and before he died Galvani showed that a contraction was possible without metals when, in a nerve muscle preparation, the free end of the nerve is placed across the muscle. In spite of this Volta's theory gained over Galvani's in this notable scientific controversy. It was not until Nobili in 1827 detected the current of injury that Galvani's claim was finally established.

work the only new experiment to be reported was one in which a hole was cut in the fore and upper part of the cranium and dura mater of a frog and another in the back of the lowest vertebrae so that a solution of opium could be injected through the canal and come into direct contact with the brain and spinal cord. In this experiment the animal was immediately convulsed; after fifteen minutes the heart beat was feeble and slow and after thirty minutes the muscles twitched feebly when the sciatic nerves were pinched and when Galvani's metallic arc was applied. The same experiments were repeated with rabbits and a pig.<sup>459</sup> Monro concluded that opium applied to the brain and spinal cord did not so completely destroy the animal as to prevent some movement of the muscle when mechanically and electrically stimulated. This was in agreement with the observations of the Italian Eusebio Valli<sup>460</sup> (1755-1816), who had

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458 Monro, A., Experiments on the Nervous System, with Opium and Metalline Substances; made chiefly with the view of determining the nature and effects of Animal Electricity. Edinburgh, 1793.

459 Ibid., pp. 9-10.

460 Valli, E., Observations sur la Physique, sur L'Hist. Naturelle et les Arts, 1792, 41, 68.

observed that nerve-muscle preparations of animals killed with opium, arsenic, powdered tobacco or hemlock contracted, when the metal arc was applied, and also with the observations of Galvani himself who found that frogs which were lethargic under the influence of opium might be excited to convulsion by touch,<sup>461</sup> Valli and Giovanni Aldini (1762-1834), nephew of Galvani, explained these observations by saying that the electrical principle was so powerful that poisons which can destroy life cannot destroy animal electricity.<sup>462</sup> Monroe, however, took the opposite view and said the observations indicated no inherent nerve forces (i.e., animal electricity) were involved at all and the responses observed were due to simple electrical phenomena.<sup>463</sup>

Monroe's studies with opium in this new work

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<sup>461</sup> Aldini, G., De Animalis Electricae Theoriae Ortu Atque Incrementis, p. xv.

This dissertation introduced a new edition of Galvani's De viribus electricitatis which was published at Modena in 1792 under the supervision of Aldini who added footnotes to the original.

<sup>462</sup> Valli, E., Observations sur la Physique, sur L'Hist. Naturelle et les Arts, 1792, 41, 74.

Aldini, G., De Animalis Electricae Theoriae, p.xiv.

<sup>463</sup> Monroe, A., Experiments on the Nervous System,  
Edinburgh, 1793, p.41.



did little to advance his thesis concerning animal electricity and added nothing to his earlier work and theories concerning the mode of action of the drug. It was, however, an opportunity to compare his own theories with those of Fontana and this appears to have been the motive for including the opium experiments. Monro agreed with Fontana that the drug or poison is absorbed, but he believed that once in the circulation the substance brought about its effects by affecting the nerves of the vessels and the heart. He disagreed with Fontana's theory of direct action on the blood or on a principle in the blood for the following reasons. First, it implies that a poison injected into a limb should act as quickly as when injected into a vessel near the heart, and he pointed out that Fontana himself had shown this to be untrue. This is not an effective argument because the theory does not imply that the poison should act as quickly, although, as William Alexander pointed out, it does mean that the poison must be ultimately as effective whether injected into a limb or into the heart. Second, animals wounded by the viper were convulsed immediately and long before the effects on the blood could have influenced the muscles. Third, when a toxic dose of cherry laurel was poured into the stomach of

pigeons, they died before it could have entered the circulation, i.e. before the normal processes of absorption through the stomach wall could have taken place. These latter reasons Monro put forward in support of action through the nerves and he attempted to clinch the argument by saying that the pain of a viper bite is proof of action on, and therefore implies action through, the nerves.<sup>464</sup>

In the same year as that in which Monro recorded these objections, his pupil, Richard Fowler (1765-1863), published his experiments with animal electricity and included also some work on opium.<sup>465</sup> Fowler argued that, if Fontana's theory was correct, then a limb deprived of blood before the administration of the drug will not be affected by it. Following this theme, he made a number of experiments which included the following. He divided the sciatic nerves in both legs of a frog (to eliminate exhaustion due to pain), then

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<sup>464</sup> Monro, A., Experiments on the Nervous System, Edinburgh, 1793, pp. 14-16.

<sup>465</sup> Fowler, R., Experiments and Observations relative to the influence lately discovered by M. Galvani and commonly called Animal Electricity, Edinburgh, 1793.

tied the crural arteries to one of the limbs, after which he injected opium solution into the skull of the animal. To observe the effects he applied the Galvanic arc in turn to each leg. He found that the contractions of the leg deprived of blood were feebler and of shorter duration than the other <sup>466</sup> He argued that the reverse should be true if Fontana was correct, and that the limb supplied with blood should be the more affected since the drug acted through the blood. In another series of experiments he deprived one of the limbs only of its nerve supply: for example, he divided the sciatic nerve in one thigh before injecting the opium into the skull. He found that, when the metal arc was applied to the limbs the leg to which the nerves had been cut continued to remain contractile for several hours after the other had become unresponsive, i.e., the opium had not affected it since the nerve through which it acts had been cut.<sup>467</sup>

The arguments of Fowler, however, are both confused and illogical; for if, as he implied, the opium acts through the nerves, then the results of the first experiment cited above are contradictory since in that

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<sup>466</sup> Fowler, R., Experiments and Observations, Edinburgh, 1793, p. 150.

<sup>467</sup> Ibid., p. 154.

experiment the sciatic nerves to both limbs were cut. Further, in a similar experiment he reported that a difference in contraction occurred between a leg with the artery tied and one with a free circulation, and yet in this case the nerves to both were intact! It would seem that Fowler was so intent on discrediting Fontana that he was blinded to the illogicality of his own arguments. He assumed that he could follow the effects of opium by noting the reaction of the muscles to the galvanic arc. But Valli, whose work Fowler had read, had reported that the limbs of animals poisoned by opium continued to contract and, therefore, in Fowler's experiments, there was no significance in the strong response of the limb to which the circulation had not been cut. Instead the significance lay in the weakened response of the mutilated limb, but Fowler makes no reference to having made experiments to observe the response of such a limb in the absence of opium.

That same year, 1793, saw yet another criticism of Fontana's theories, this time from the young Irish physician Samuel Crumpe (1766-1796). Crumpe rejected the theory as an 'antiquated belief' and said that the blood was a simple circulating fluid carrying, nutrient, heat and waste materials and that it did not possess that

living principle which Hunter and Fontana claimed.<sup>468</sup> In answer to Fontana's work showing that opium did not act through the nerves, he argued that in the circumstances of the experiments the nerves were not properly 'organised' and there was no more reason to suppose that the body of the nerve would convey the effects of opium than that the body of the optic nerve would perceive light.<sup>469</sup> Fontana's conclusion that opium attacks the blood because, on injection, it brings about immediate convulsions, is opposed by the strong argument that it had already been shown that even the most innocent of substances would cause violent convulsions on injection into the jugular vein.<sup>470</sup> These were sensible and logical arguments in opposition to Fontana and it is indeed unfortunate that Crumpe instead of resting content with this went on to put forward his own theories, which only added further confusion to a confused subject.

Crumpe supported the Whytt and Monro theory of action through the nerves and held that the drug on injection into a vein affected a plexus of nerves on the inner

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<sup>468</sup> Crumpe, S., An Inquiry into the Nature and Properties of Opium, London, 1793, pp. 103-125.

<sup>469</sup> Ibid., p. 127.

<sup>470</sup> Ibid., p. 130.

lining of the vessel. He supported this idea with some experiments of his own. In one, the limb of a frog was dissected so that it was attached to the trunk only by the bone and the large nerves. Opium was injected under the skin of the dissected limb. He notes that the animal died in one hour, the same time as for an undissected frog injected in the same manner. To eliminate the possibility that the result was due to the dissection, he treated a frog in the same manner but omitted to inject the opium. It survived seven hours.<sup>471</sup> Crumpe described this work as his experimentum crucis, and claimed to have repeated it several times. Nevertheless, only two experiments are actually recorded and in neither case did he specify the precaution taken in the dissection to eliminate all possibility of absorption. However, he went further than action through the nerves to explain the action of opium, putting forward a theory having its origins in the physiology of John Brown and William Cullen, which was that the vital solids of the body are endowed with a principle termed excitability, which responds to exciting and stimulating powers.

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Crumpe, S., An Inquiry into the Nature and Properties of Opium, London, 1793, p. 137.

Crumpe regarded opium as a stimulant for this excitability and a number of arguments are put forward in support. First, that it is dangerous in inflammations (still a matter of controversy at that time); second, an addict to opium can obtain relief only in another stimulant, e.g., wines and spirits; and third, it affects the pulse. This last statement is based on an experiment in which he took a one-grain dose of opium and noted an increase in his pulse-rate when taken at five-minute intervals. The results as recorded are as follows:

Min.	2	5	10	15	20	25	30	35	40	45	50	55
Pulse	70	74	76	76	74	74	74	72	72	70	70	70. <sup>472</sup>

He resorts to an ingenious argument to explain how a stimulant can exert the narcotic effects exhibited by opium. He suggests that the stimulant power is suddenly exhausted, leaving the body insensible to the normal stimulant and exciting powers, since these are inferior in power to that of which the system has been recently deprived, an effect analogous to that when a man, having looked at the sun, finds himself for a time blind to all other objects.

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<sup>472</sup> Crumpe, S., An Inquiry into the Nature and Properties of Opium, London, 1793, p. 33.

In 1795 Alexander Philip Wilson (1770?-1851?), physician in Edinburgh, made a valuable contribution to the experimental knowledge of the action of opium on the living body in a work published under the title: An Experimental Essay on the Manner in which Opium acts on the Living Body (Edinburgh). Philip Wilson, who later became known as Alexander Wilson Philip, was a prolific writer on medical subjects (Munk lists 15 books) and achieved a reputation as physiologist and practitioner.<sup>473</sup> The opium studies were among his earliest work and he brought a fresh and open mind to this by now confused subject. His Essay contains not only a report of his own experiments, but also a lucid survey of the principal experimental studies carried out to that time and a statement concerning the contradictions involved in the explanations which had been put forward. Among the contradictory facts reported in earlier work he noted the following. Opium was said to affect the nerves of the abdomen, stomach and heart,

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<sup>473</sup> His career ended tragically. As a result of injudicious investments he was in danger of a debtors' prison and he was forced to leave London in 1843. There is no further trace of him and his death is assumed to have occurred in 1851 when his name ceased to be entered as a member of the College of Physicians.



and to act on other parts of the body by sympathy even when the circulation was interrupted. Opposed to this were reports that opium does not affect the body when applied to the nerves of the extremities. Again, opium taken into the stomach and intestines was said not to affect the heart, while it was also said that the solution injected directly into the abdominal cavity affected that organ so quickly that its action could not have taken place via the absorbents. But, Wilson asked, if it affects the heart and body through the nerves when injected into the abdominal cavity why does it not do so in the stomach?<sup>474</sup> Philip Wilson, on the basis of his own experiments attempted to resolve these contradictions in the literature by the following propositions:

- (i) that opium enters into the circulation and is carried to the brain and so exerts its effects on the muscles,
- (ii) it has a local effect upon the circulation,
- (iii) its effects are on the voluntary muscles only and not on the heart or intestines, and
- (iv) it has only a local effect on the nerves at the site of application.

In an early experiment Wilson had noted that

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<sup>474</sup> Philip Wilson, Experimental Essay, Edinburgh, 1795,  
p. 41.

a solution of opium injected directly into the heart was passed along the aorta towards the head (the passage of the dark brown solution along a blood vessel would be easily observable). This suggested to him that the convulsions that followed the injection did not result from a sympathetic action of the nerves of the body with the nerves of the heart, but from the result of the direct application of the drug itself to the brain. To investigate further, he ligatured the aorta of twelve frogs before injecting a strong solution of opium<sup>475</sup> into the heart. He reported that the heart ceased to move immediately, but that no convulsions took place and the irritability of the muscles was found to be similar to that in frogs which had died after removal of the heart.<sup>476</sup> Similar results were obtained when the aorta was divided. An obvious objection to this experiment is that the absence of convulsions was due, not to the opium being unable to reach the brain, but to the interruption of the

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<sup>475</sup> The strong solution of opium was prepared as follows: one ounce of opium was triturated with three fluid ounces of water. The mixture was placed in a container and exposed to a temperature of 90°F for 12 days, before filtering. (Philip Wilson, Experimental Essay, Edinburgh, 1795, p. 47).

<sup>476</sup> Ibid., p. 48 .

circulation. To counter this suggestion Wilson performed the following control experiment. The aorta of a frog was secured by a ligature and the opium solution was dropped into the brain through an opening in the skull of the animal. Violent convulsions of the muscles followed and afterwards it was found that the irritability was 'much impaired'.<sup>477</sup> No theories are put forward by the author concerning the exact nature of the action on the brain. He simply observes that, when the drug is freely applied to that organ, it causes convulsions and death, i.e. effects which normally follow a violent irritation of the brain. This is not to suggest that opium is a common irritant; for Wilson later attributed some specific effects to the drug:

" the convulsions produced by opium, it has been shown, are of a peculiar kind. In each of its effects on the living animal, we still find that opium has much in common with other substances, but, at the same time, some thing peculiar to itself." <sup>478</sup>

The second proposition concerning the action of

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477 Philip Wilson, Experimental Essay, Edinburgh, 1795,  
p. 55.

478 Ibid., p. 102.

opium arose from a consideration of Monro's work. Monro had reported that opium injected into the abdominal cavity of a frog affected the motion of the heart, and he concluded that this effect must be brought about through the medium of the nervous system. Fontana on the other hand had shown that the drug given by mouth did not affect the heart and that none of its effects were by sympathy of the nerves. To explain these contradictions, Wilson suggested that opium applied directly to the blood vessels destroyed their 'muscular power' and by being so applied by Monro to the great vessels of the abdominal cavity so affected the circulation as to alter the motion of the heart.<sup>479</sup> The principal experiment to support this explanation was one in which he observed the circulation in the web of a frog's foot after the injection of opium solution under the skin. He reported that after a time the circulation became 'languid' and that after 2 to 3 minutes the movement of blood ceased. He notes that this effect was not due to the systemic effects of the drug because no changes were observed in the motion of the blood in the other foot.<sup>480</sup> Thus Wilson believed in the

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<sup>479</sup> Philip Wilson, Experimental Essay, Edinburgh, 1795, p. 59.

<sup>480</sup> Ibid., p. 60.

the immunity of the heart to the effects of opium and he demonstrated this by observing the heart after the drug had been applied to the brain and spinal cord. In one of these experiments he followed the technique of Monro, making a hole in the cranium and the lower part of the spine and injecting the opium through the cavity. Before the injection the thorax was opened and the motion of the heart carefully observed. In the seven frogs used, all the animals were instantly deprived of all voluntary motion and appeared to be dead "but the motion of the heart was not in the least affected".<sup>481</sup> This mode of application was determined by Wilson's belief that the drug was received into the circulation and carried to the brain. The exclusive use of this technique of direct application to the brain through an opening in the head, however, was unfortunate, not only because of its artificiality, but also because Wilson actually demonstrated himself that the same effects were produced by simple mechanical irritation of the brain.<sup>482</sup>

A similar technique was used on rabbits to

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<sup>481</sup> Philip Wilson, Experimental Essay, Edinburgh, 1795,  
p. 79.

<sup>482</sup> Ibid., p. 80.

observe and determine the effects of opium on the peristaltic movements of the intestine. He found that opium applied to the brain does not appear to effect peristalsis, although other voluntary muscles were strongly convulsed.<sup>483</sup>

Kraau Boerrhaave and Haller had demonstrated that opium given internally does appear to affect the movements of the bowels, and in his next experiments Wilson demonstrated that this was in fact due to a local action on the inner surface of the intestine. He applied the solution to the outer surface of the gut without any noticeable effect but, when he injected it through the wall of the intestine, the peristaltic movements were stilled. To this local action he attributed the 'costiveness' (constipation) of patients treated with opium.<sup>484</sup>

These latter observations were the basis for the third proposition that the drug affects the voluntary muscles only and (in support of Haller and Fontana) does not affect the heart. That the voluntary muscles were convulsed had, of course, never been in doubt, but there were contradictory reports concerning the effect on the

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<sup>483</sup> Philip Wilson, Experimental Essay, Edinburgh, 1795,  
p. 82.

<sup>484</sup> Ibid.

irritability of the muscle. Fontana had reported experiments which indicated that the irritability of the muscle was but slightly affected. Alexander on the other hand had reported some work which suggested they were completely deprived of their irritability. Wilson, who appears to have been a careful worker, was unable from his own experiments to subscribe to either of these extreme opinions. In his own experience he found that, where convulsions had taken place, the irritability was impaired (but not exhausted) but, where there were no convulsions, irritability was not affected. He was, therefore, led to conclude that the impairment of irritability was due to the convulsions and not to the drug. He devised an experiment to confirm this. He took two frogs of equal size and age and into each he injected the solution of opium. After the initial convulsions, one of the animals was carefully isolated to protect it from any stimuli that might excite further convulsions. The other subject was repeatedly stimulated so that the animal was kept in a permanent state of convulsions. He discovered that in this latter animal irritability was impaired to a greater degree.<sup>485</sup>

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<sup>485</sup> Philip Wilson, Experimental Essay, Edinburgh, 1795,  
p. 104.

In his discussion of this experiment Wilson makes some interesting observations on the techniques used in these studies. He observed that tests for irritability were crude, unreliable and contradictory; for example, muscles brought to some slight movement by mechanical stimulation did not always respond to the galvanic arc. In addition, reported changes in irritability might also be due to the conditions under which the nerve and muscle are exposed, the age and condition of the frog and the exact manner in which the animal dies, i.e., with or without prolonged convulsions. It is obvious, therefore, that Wilson appreciated that changes observed in nerve-muscle responses might be due to a number of factors apart from the drug, and that this might lead to a false conclusion. Fontana also realized this danger and had introduced as many controls as possible, a feature of experiment which Wilson does not always follow.

His omission of the control experiment is most obvious in the investigations to establish his fourth proposition, which was that opium acts in the same manner as other 'topical irritations', i.e., acting on the nerves at the site of application. In this experiment the hearts of 24 frogs were cut out and different quantities of opium solution were injected into the abdominal cavity



of each. None of the animals was convulsed; instead, they became languid in a degree proportional to the dose administered. In all cases they could be stimulated to a contraction after death.<sup>486</sup> Wilson chose to use this result as evidence for a local effect upon the nerves, noting that in this case the absence of convulsions excluded a general systemic action. Unfortunately, he made no controls and did not indicate the reaction of a frog similarly dissected, but not exposed to the action of opium. Thus the final proposition that opium has a local effect upon the nerves was not supported by valid experimental evidence.

As a result of these experiments with solutions of opium and with similar studies with an infusion of tobacco,<sup>487</sup> Wilson suggested that poisons and drugs might be divided into two classes. Substances in the first class are absorbed into the circulation and are carried to the brain, their effects being upon the voluntary muscles only. These substances when they act

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<sup>486</sup> Philip Wilson, Experimental Essay, Edinburgh, 1795, p. 89 et seq.

<sup>487</sup> Ibid., p. 143, Appendix. Experiments made with a view to determine the manner in which Tobacco acts on the Living Animal.

upon the nerves at the site of application produce effects not essentially different from those produced by any strong topical irritant. They produce no other effect through the medium of the nerves, and their effects upon the body when applied to a wound differ only in degree from those produced when it is injected directly into the cavity of the body. The majority of poisons including opium, were in this class. The second class included those substances that do not affect the sentient extremities of the nerves in the sound state but, when applied to lacerated nerves, produce effects essentially different from those of mere topical irritation. This group was said to include the viper poison and the poison of a rabid animal.<sup>488</sup> The reason for putting these poisons in a separate class does not appear to be simply that they acted through lacerated nerves (which was mere assumption and contested by the experiments of Fontana), but because their rapid and violent effects were produced only when they were injected into a wound in the flesh and, therefore, they were obviously different from substances in the first group.

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<sup>488</sup> Philip Wilson, Experimental Essay, Edinburgh, 1795, p. 161.

Philip Wilson in this work clearly indicated the contradictions inherent in, and the confusion surrounding, the pharmacology of opium. In an attempt to resolve the contradictions, he made a number of experiments which led him to the conclusion that the drug is absorbed into the circulation and carried to the brain before it exerts its systemic effects, and that any direct effect upon the nerves was purely of a local character. Although he came nearer to the truth than his predecessors in this field of study, his experiments were not designed to remove the principal objections to such a theory, i.e., the rapidity of action which appeared to exclude the possibility of a preliminary absorption, and the minute apparently ineffective quantity which appeared to be absorbed from the stomach. Both of these objections, of course, strongly supported the theory of action through the nerves. Furthermore, the experiments which Wilson did describe were not so conclusive as to be acceptable without reservation in the face of the alternative theories put forward by Whytt, Monro, Fontana, Alexander and others - a fact which he appeared to recognize when he describes his ideas as simple alternatives put forward to resolve the obvious contradictions. Nevertheless, they were ideas based on experiment, and the whole work serves to

illustrate that in the last decade of the eighteenth century the method of animal experimentation had become a recognized and established procedure for pharmacological and toxicological investigation.

(vii) The Recognition of the Place or Role of the  
Experimental Method in Pharmacology.

In 1781, at the time of the publication of Fontana's Traité, experiments on animals with drugs and poisons had been reported from the principal centres of medical learning: Leyden, London, Edinburgh, Paris, Bologna, Göttingen and Vienna. In the work published it is possible to distinguish:

- (i) the introduction of new techniques arising from contemporary developments in anatomy and physiology,
- (ii) the development of the principle of standardization of substances under test and of regulated dose (within the limits imposed by the nature of the materials),
- and (iii) the recognition of the variability of results and possible errors in experiments with living animals.

It cannot be claimed that these studies had an immediate effect upon contemporary therapy and they must be judged academic when compared to the work of Withering or Stoerk. At the same time, however, this work may be justly regarded as forming a basis for future progress in pharmacology. To fully evaluate this development it is first necessary to consider opinions concerning the validity of animal experiments when applied to human medicine.

Doubts concerning the application of the knowledge of the effects of drugs on animals to man continued to be expressed in the early part of the eighteenth century. The arguments were the same as those put forward in the seventeenth century, for example, François Boissier Sauvages de la Croix (1706-1767), Professor of Medicine in Montpellier, in his memoir Observations sur quelques Plantes Venimeuses,<sup>489</sup> rejected the method of animal experiment on the slender argument and doubtful fact that bitter almonds (amandes amères) and Parsley (le Persil), although food for man, are poisonous to birds. For some physicians 'facts' such as this rendered a direct comparison between the reactions of animal and man to be impossible. Others, however, were beginning to modify their views.

In 1746 the English physician Brown Langrish published his Physical Experiments upon Brutes (London) in which he wrote:

"By a series of Experiments, and a long Experience of the good or bad Qualities of any Drug upon Brutes, we may investigate, in a great Measure, its Nature, and what Effects it

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<sup>489</sup> Mém. Acad. R. Sci., 1739 (pub. 1741), p. 469.

it likely to produce in human Bodies." 490

On the subject of the validity of animal experimental results being applied to man, Langrish did not reject completely the arguments put forward by de la Croix and others. He admitted that certain substances are dangerous to man and apparently not to animals and vice versa but at the same time he believed this objection to be eclipsed by the obvious fact that "the greatest Number of Medicines affect both equally".<sup>491</sup> He was unable, however, to give evidence in support of that statement. Langrish regarded experiments on animals<sup>492</sup> only a preliminary to experiments on man as a means of discovering which substances might be tried to greatest advantage on human beings and as a means of protecting human subjects from the more dangerous substances. The ultimate aim was to make careful experiments to observe the effects of a drug upon men using such materials "whose Efficacy and Safety they [the physicians] had often tried beforehand upon Brutes".<sup>492</sup> Langrish, whose inspiration was derived from Bacon's New Atlantis, proposed the setting up of a Commission appointed by the Royal Society or College of

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490 Langrish, B., Physical Experiments, London, 1746,  
p. 120.

491 Ibid., p. 56.      492 Ibid., p. 120.

Physicians which would be responsible for pharmacological and toxicological experiments. It was necessary in his opinion to confirm on human subjects the results of experiments on animals and such a study could only be carried out by a carefully controlled officially appointed body. He suggested that convicted felons be sent to the Commission for the purposes of experiment and exhorted it to be:

"humane, charitable and good natured; so that no hardship would be put upon the Subjects under their care, no such Experiments made, as would put them to unnecessary Pain or endanger their Lives." 493

Although this suggestion to invest a Commission, however, responsible it might be, with such powers over human beings is in itself repugnant, it cannot be denied that Langrish's concern for the treatment of the criminals is humane and more considerate than the treatment commonly extended to them at that time.

Halfway through the eighteenth century the question of the validity of animal experiments in respect to human beings was invoked in the field of pure

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493 Langrish, B., Physical Experiments, London, 1746,  
p. x.



physiology. The studies of irritability, sensibility, voluntary and involuntary motion, conducted by Whytt, Haller, Zimmerman, Fontana and others, were associated with a large number of animal experiments. In Haller's second *mémoire* "Sur les parties Sensibles & Irritables du corps humain",<sup>494</sup> 557 experiments are reported, 9 of them human, the remainder on animals, including frogs, rabbits, dogs, cats, sheep, rats, mice, hedgehogs, eels and birds. Anton de Haen, physician in Vienna, a quarrelsome man who believed in the superiority of clinical experience over physiological experiment, opposed Haller's conclusions and in doing so drew attention to the small number of experiments carried out on humans compared with the great number of animal studies. He argued that the inferences drawn by Haller from his work were not valid because men and brutes differ entirely in their nature.<sup>495</sup> Haller, in a sharp reply to de Haen ([You] "impute to me errors I never thought of, in order to have something to censure"<sup>496</sup>) defended his experimental results, but did not take up the question of their validity when applied to human beings.

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<sup>494</sup> Haller, A. von, Mémoires, Lausanne, 1756, Vol. I, p. 101.

<sup>495</sup> Haen, Anton de, Medical Museum, 1763, I, 166.

This question, however, had already been posed and answered by the Swiss physician, Simone André Tissot (1728-97), in a preface to Haller's own Mémoires sur la nature sensible et irritable, des parties du corps animal (Lausanne, 1756). Tissot reminded those who opposed the use of animal experiments that most of the successful physiology arose from this source and he quoted the examples of the circulation of the blood and physiology of respiration. Tissot believed animal experiments to be acceptable

" because we cannot be deceived as to the perfect uniformity of the mechanism in us and in brutes, with regard to the vital and natural functions; for that is demonstrated by the exact resemblance of similar parts and of the essential organical parts".<sup>497</sup>

Here the phrase uniformity of mechanism is significant.

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<sup>496</sup> Haller, A. von, Medical Museum, 1763, I, 377, et seq.

<sup>497</sup> 'parce qu'on ne peut pas se faire illusion sur la parfaite uniformité de leur mécanisme, par rapport aux fonctions vitales & naturelles; elle est démontree par l'exacte ressemblance des parties simillaires, & des parties organiques essentielles.'

Tissot in Haller's Mémoires, Lausanne, 1756,  
Vol. I, p.xli.

Tissot argued in respect of this that the crane that lifts a beam of wood or a block of marble is the same crane and operates in the same manner on each occasion and thus one can argue that the mechanism of circulation is the same in animals as in man. The analogy, however, was not so obvious in respect of the doctrines put forward by Haller, which concerned sensibility, and the question of voluntary movements. One of de Haen's principal objections concerns the application of results concerning sensibility from brutes to rational creatures, i.e., men with control over their reactions.<sup>498</sup> We did find some support for this argument in Tissot's own preface when he says that, although the principle of sensation is the same in both, in the beasts the response is mechanically determined, but in man it is influenced by the soul.<sup>499</sup> A not dissimilar problem was associated with studies in pharmacology and toxicology. There had never been any doubt that corrosive minerals exerted their mechanical and chemical effects on the tissues and organs of men and animals alike. The problem lay, however, with narcotics such as opium, and poisons such as cherry laurel

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<sup>498</sup> Haen, A. de, Medical Museum, 1763, I, 166.

<sup>499</sup> Tissot in Haller's Mémoires, Lausanne, 1756, Vol.I, p. xlv.

where the brain, nerves and associated organs were involved but without apparent damage.

This was the background against which Monro, in 1761, published his experiments concerning the mode of action of opium, camphor and alcohol. Monro's subject for these studies was the frog and he felt it necessary to refer to doubts that might arise concerning the propriety of applying to human physiology results obtained from studies of an animal so very different from man. His argument in favour of his methods was simply to distinguish between degree of action and mode of action. The effects of medicine, he said, may be quicker and more violent in one species than in another, just as they may differ between men of strong and weak constitutions; he could not, however, agree to there being any difference between mode of action. He repeated Tissot's arguments:

"if two species of animals, provided with like systems of nerves and vessels, suffer in a similar way from the application of the same medicine; and if this medicine can be proved to affect one species solely through the nerves to which it was primarily applied, or solely after being absorbed and mixed with the blood; it may be supposed to affect the other in the same manner." 500

In the same year as that in which Monro published his experiments, William Lewis cautiously recommended animal experiments as a means for the investigation of drugs that could not be studied by any other method, i.e., by botanical affinity, by chemical analysis or by a study of sensory characters. These drugs included the narcotics, emetics and purgatives, drugs which "operate by some latent power, of which they give little or no intimation to the senses".<sup>501</sup> In fact, Lewis was admitting that it was the only method that could lead to a true knowledge of pharmaco-dynamic action. The alternative, although essentially similar, method was to experiment directly upon man and some physicians and students in the eighteenth century undertook this hazardous course. Samuel Bard, an American pupil of Monro, in preparation for a doctoral thesis on the properties of opium, swallowed the drug and endeavoured to confirm its stimulant properties by recording the pulse-rate.<sup>502</sup> In order to be more objective, he repeated the experiments upon a fellow student,

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<sup>500</sup> Monro, A., Essays and Observations, Edinburgh, 1771, 3, 294.

<sup>501</sup> Lewis, W., Materia Medica, London, 1761, p. x.

<sup>502</sup> Bard, S., De Viribus Opii, Edinburgh, 1765, p.18  
et seq.

who extracted from him a promise that he would himself become a subject for experiment. In fulfilment of this promise Bard allowed himself to be subjected to the effects of ammonia, which, it is reported, caused him some discomfort!<sup>503</sup> In 1768, also at Edinburgh, William Alexander (d. 1783), a physician, investigated the doses of a number of common medicines by self-administration, which he believed to be the only sure way to a knowledge of the virtues and effects of medicines.<sup>504</sup> The dangers of this method are all too apparent in this work by Alexander. One of the medicines he chose to study was camphor and, after some preliminary studies with small doses, he increased the dose to 40 grains. After some extremely unpleasant symptoms he became delirious and, since he had informed no one of his intentions, his servants and colleagues were mystified by his condition. William Cullen apparently left without being able to help, but Monro took the trouble to search the room and coming upon Alexander's notes discovered that the patient was poisoned.

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<sup>503</sup> M'Vickar, J., The Life of Samuel Bard, New York, 1822, p. 74.

<sup>504</sup> Alexander, W., Experimental Essays, II, On the Doses and Effects of Medicines, London, 1768, p. 78.

Fortunately, the discovery had been made in time and, after the patient had been made to vomit, he slowly recovered.<sup>505</sup> Needless to say, this experience brought to a sudden end the experiments with doses.

Another worker to investigate the action of a drug by self-administration was John Leigh, who studied the effects of opium solution injected into the urethra.<sup>506</sup> Leigh also records a number of experiments carried out on healthy men with the resin extracted from opium. He records also that he administered 5 grains of the resin to a patient, a man of thirty years, who as a result suffered nausea, a raving-like drunkenness, thirst and copious discharge of urine.<sup>507</sup> It is not said whether this was by way of treatment or experiment! Except for considerations of dose, none of these experiments display any outstanding advantage over similar studies with animals.

Fontana whose work was purely toxicological had

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<sup>505</sup> Note: A record of these experiences were the subject of a paper read to the Royal Society in 1767. see Phil.Trans., 1767, 57, 65.

<sup>506</sup> Leigh, J., An Experimental Enquiry into the Properties of Opium, Edinburgh, 1786, p.100.

<sup>507</sup> Ibid., pp. 110-111 .

no alternative but to work with animals. He does not appear, however, to have had any doubts concerning the validity of his results with animals when applied to man. He observed that the effects on one species were the same as those on another, that the effects were proportional to the dose, and that the dose was proportional to the size of the animal. He did not doubt that the analogy between the effects of a poison on man and the effects on a warm-blooded animal was perfectly admissible<sup>508</sup> and, as we have seen,<sup>509</sup> he extended this analogy quantitatively to predict, on a weight basis, the fatal dose of a poison for a man. Fontana's enthusiasm for this method was not shared by Withering, who in 1785 rejected the method of animal experimentation for a study of digitalis "because it has not been much attended to".<sup>510</sup> Shortly after, however, Cullen wrote<sup>511</sup> that he regarded it as a proper measure for the investigation of new substances, although he cautiously observed that the difference in the degree of activity between species may give rise to different

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<sup>508</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p.36.

<sup>509</sup> See p.220 above.

<sup>510</sup> Withering, W., Account of the Foxglove, Birmingham, 1785, p.1.

<sup>511</sup> Cullen, W., Treatise of the Materia Medica, Edinburgh, 1789, Vol. I, p. 153.



effects, and he, therefore, recommended that the results of such experiments must be confirmed upon the human body.

To summarize the situation in the last decades of the eighteenth century, it may be said that experiments on healthy animals were now recognized as a legitimate means of study to discover the effects of drugs, and indeed as the only means for an objective study of the ~~the~~ action of poisons. The reports already published on such experiments with drugs and poisons together with contemporary developments in comparative anatomy and physiology<sup>512</sup> supported the view that the results were valid when applied to man, but as yet there was no general proof of this. What proof there was existed largely in the observations of the extreme toxic effects of known poisons or of excessive doses of medicines, where the effects of such substances administered deliberately or by accident to men and women were reproducible in animals.

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<sup>512</sup> Contemporary opinions on the rational basis of comparative anatomy in the 17th and 18th centuries have been recorded by F.J. Cole in the introduction to his A History of Comparative Anatomy, London, 1944. It will be noted that John Hunter (1728-1793), the most celebrated anatomist of his day, accepted man as the ~~central object~~ <sup>standard reference</sup> with whom other types are to be compared.

There was, however, at least one classic example of experimental pharmacology which was to find an application in human medicine. In 1776 a young German, Peter John Andrew Daries, studying in Leipzig, wrote a thesis on the belladonna plant.<sup>513</sup> Earlier in his career, when he was working with an apothecary, a fragment of belladonna extract entered his eye and impaired his vision. As a result of this experience when preparing his thesis, he made some experiments with the plant on the eyes of cats. He placed the expressed juice of the herb into the right eye of the animal and the juice from the fruit into the left eye. He observed the dilation of the pupil which resulted from the administration of the drug and the duration of the mydriatic effects.<sup>514</sup> The practical application of this discovery was made by the German physician, Johann Albert Heinrich Reimarus (1729-1814), who, learning of this work, discovered that by the use of this drug the whole of the lens is rendered distinct, with the result that he put the drug to use in operations for cataract.<sup>515</sup> In belladonna, we have an example of the demonstration, by experiment,

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<sup>513</sup> Daries, P.J.A., De Atropa Belladonna, Lipsiae, 1776.

<sup>514</sup> Ibid., p. 37.

<sup>515</sup> see London Medical Gazette, 1845, I (new series), 185.

of a specific effect which found an application in medicine. On the other hand, we also have the example of opium which, although widely studied experimentally and commonly used in practice, remained the subject of considerable discussion, controversy and confusion concerning its mode of action, site of action and even specific effects. Similar discussion and arguments were associated with other substances, e.g. preparations of cherry laurel and the arrow-poisons. The controversies associated with these drugs and poisons illustrate the fact that, although at the end of the eighteenth century, animal experimentation was an established procedure, for which a number of techniques had been developed and methods discussed, further advance towards a true pharmacology, i.e., quantitative pharmacodynamics, was limited. At this time two difficulties had to be overcome before there was a further significant advance in this field. They arose (i) from the fact that, owing to the raw and crude nature of many of the drugs and poisons, it was not possible to expect uniformity of reactions or reproducibility of results, since there was no way of ensuring an exact dose of the active principles in the drug or preparation and (ii) from the circumstance that knowledge concerning the mode of administration and the

recognition of specific sites of action was confused by the controversy as to whether the drug could act directly through the nerves or by means of the circulation after absorption. Both of these problems, that of dose and that of mode or route of action, were resolved by developments in the first decades of the nineteenth century.

#### 4. DEVELOPMENTS IN KNOWLEDGE OF DOSE AND EFFECT

Physicians throughout the history of their art have administered medicines to their patients in measured doses. It is, therefore, not surprising to find this factor carefully observed in the early pharmacological experiments. So little was known, however, concerning the nature, constitution and route of action of the drugs, that a knowledge of the quantity administered, frequently had no meaning at all. For a further development of pharmacodynamics it was necessary for physicians to reach an appreciation of the activity of a drug or poison in terms of its active constituent and of the effects it produced in the body.

At the beginning of the eighteenth century three important principles of posology had been expressed. First, it was emphasized (as doubtless it had often been in earlier times) that care must be exercised when administering active medicaments. John Quincy (d. 1722) writing on this subject said:

"And as herein [in acute cases of illness]  
Medicines of efficiency are concerned, they are  
most safely distributed into Boles, or Draughts,  
that the patient may not be trusted to guesswork

but that the dose may be ascertain'd to the greatest exactness, and especially when Opiates are us'd." 516

The second principle was that the dose must be regulated according to the age and condition of the patient and this was expressed in the early eighteenth century in the work of William Cockburn (vide infra). The third and most significant in this age of polypharmacy was that the dose of a preparation must be related to the concentration of its active constituent. This latter feature may be illustrated by a quotation from the work of the empiric William Salmon (1644-1713), who wrote:

"But Considered as they [cathartics and emetics] are compounded, the Dose must be limited by those of the Simple, in respect of what the Sum of all the Purging Parts, bear to the sum of the whole Composition." 517

These principles were valuable safeguards but their full application was limited by an ignorance of the nature of the action and constitution of the drugs themselves. For this reason general posology did not advance

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516 Quincy, J., Pharmacopoeia officinalis, London, 1719  
2nd ed. , p. 618.

517 Salmon, W., Synopsis Medicinae, London, 1695 »3rd  
ed., p. 324.

to any appreciable degree for the greater part of the century. Lists of doses were often given, but in the majority of cases they were concerned only with cathartic and emetic substances. These guides exhibited wide ranges of dose for individual drugs and, with the notable exceptions of the extensively used opium and ipecachuanna,<sup>518</sup> all were in excess of modern standards (see Table XIV). The official recognition of doses was long delayed, in Great Britain, for example, comprehensive dose lists appeared in certain translations of the pharmacopoeia<sup>519</sup>

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<sup>518</sup> Ipecachuanna root was introduced into Europe from South America in 1672 by the French physician, Le Gras. A quantity of the drug came into the possession of the Dutch physician, Jean-Adrien Helvetius (1661-1727), who used it to treat dysentery and sold it in Paris as a 'secret' remedy. It is reported that it cured the Dauphin and other gentlemen of the Court with the result that trials were carried out at the Hôtel Dieu, the success of which induced Louis XIV to purchase the remedy from Helvetius for 1000 louis d'or. After this transaction the name of the remedy was made public.

See Flückiger and Handbury, Pharmacographia, London, 2nd ed., 1879, p. 371.

Pereira, J., Materia Medica, London, 3rd ed., 1850, vol. ii, p. 1591.

<sup>519</sup> See Richard Powell's translation of the London Pharmacopoeia, 1809.

Table XIV. Doses recommended in works published during the 17th, 18th and 19th centuries.

(Note. Doses are given in grains.)

	(1) 1668	(2) 1708	(3) 1719	(4) 1749	(5) 1762	(6) 1775	(7) 1815	(8) 1867	Modern doses
Aloes	20:60:120	60	30	20	6-60	5:20:60	5-15	2-6	2-5(9)
Calomel	-	-	20	-	-	2, 6:10	5-15	$\frac{1}{2}$ -5	$\frac{1}{2}$ -3(9)
Colocynth	6:10:20	6	-	-	-	-	1-5	-	2-5(11)
Hellebore nig.	15:20:40	-	15-20	20	-	-	10-30	-	-
Ipecacuanha	-	30	10-40	40	4-20	10:20:40	5-30	5-30	15-30(10)
Jalap	20:90:120	30	30-60	30	6-20	10:20:60	10-30	10-30	5-20(10)
Rhubarb	60:90:120	60	10-40	60	-	10:30:60	10-30	5-20	3-15(13)
Scammony	6:12:20	6	20	8	6-20	5:10:15	-	-	-
Tartar emetic	-	3	3-15	-	-	$\frac{1}{4}$ : 1:5	1-3	1-2	$\frac{1}{2}$ -1(9)
Opium	-	-	-	1	$\frac{1}{2}$ -2	-	$\frac{1}{2}$ -5	$\frac{1}{2}$ -2	$\frac{1}{2}$ -3(12)

- (1) Pharmacopoeia Bateana, 1688.
- (2) Phil. Trans., 1708, 26, 50 (W.Cockburn).
- (3) Pharmacopoeia officinalis, 1719, (J.Quincy).
- (4) Linnaeus, Materia Medica, 1749.
- (5) Baumé, Éléments de Pharmazie, 1762
- (6) Practice in British and French Hospitals, 1775.
- (7) London Pharmacopoeia, 1809 (Powell's translation, 1815)
- (8) British Pharmacopoeia, 1867.
- (9) Martindale's Extra Pharmacopoeia, 1958.
- (10) British Pharmacopoeia, 1914.
- (11) British Pharmacopoeia, 1932.
- (12) British Pharmacopoeia, 1948.
- (13) British Pharmacopoeia Codex, 1949.



and in non-official dispensatories<sup>520</sup> at the beginning of the nineteenth century, but doses were not given official sanction until 1867 in the second edition of the British Pharmacopoeia.<sup>521</sup>

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- 520 The New Dispensatory, London, 6th edition, 1799. In this work the doses are included in the index to drugs and preparations. The Edinburgh New Dispensatory, Edinburgh, 2nd edition, 1804; Here the doses are given in a separate Posological and Prosodial Table.

These two important works were closely related. The New Dispensatory by William Lewis was first published in 1753. After his death independent revisions were made in London and Edinburgh. To distinguish the latter from the original London edition, it was renamed The Edinburgh New Dispensatory. In 1803, following a new edition of the Edinburgh Pharmacopoeia, Andrew Duncan, the younger, whose father had been associated with earlier revisions, completely revised the Edinburgh Dispensatory, which soon became generally known as Duncan's New Dispensatory.

- 521 The first British Pharmacopoeia was published in 1864 and was an amalgamation of the London, Edinburgh and Dublin Pharmacopoeias. The first edition did not meet with the general approval of the profession, and three years later (1867) a second edition was prepared. On pp. ix-x of the Preface to the new edition it is noted that average doses of the more important medicines are included for the first time "in compliance with a generally expressed wish."

The nature of general practice in the eighteenth century was not conducive to a rapid progress in posology. Other influences, however, were at work and these were eventually to establish the basis for a study of true dose-effect relationships. These influences may be examined and elucidated by a study of the development of the three factors essential to the progress of posology. These factors are: (a) the standardization of drugs and preparations so that the strength will not vary with the time and place of harvesting (in the case of vegetable drugs) or of manufacture; (b) experiments and clinical trials which are necessary to relate dose to the effect produced and to determine toxicity and lower limits of efficiency; and (c) a knowledge of the active constituents of a drug and the ability to extract that constituent in a pure state.

i. Standardization of Drugs and Preparations

The effective standardization of drugs and preparations may be said to have begun with the publication of the first officially recognized pharmacopoeias, the object of which was to bring some uniformity to therapeutic substances. In the pharmacopoeias of the 16th and 17th centuries formulae were recorded, the nature of vegetable drugs detailed, i.e., whether root, leaf or bark and the preparation of chemical medicines described. In the 18th

century this form of standardization improved with successive editions of the pharmacopoeias.

The importance of a standardized solution or preparation was appreciated by the majority of physicians who published the results of their experiments with drugs and poisons in the 18th century. Alston, Whytt, Fontana and Philip Wilson all recorded the strength of the opium solution they used. Maddern, Mortimer and Langrish adopted a standard method to prepare a distillate of the Cherry-laurel leaves. The last named, when weighing the leaves, reported that he did so carefully lest he might be deceived "by different measure in future Tryalls". Stoerk and Withering were both careful to describe in detail the plants they were studying as well as their method of collection and preparation. An example of careful standardization with regard to dosage is to be found in the work of a contemporary of Withering, Thomas Fowler (1736-1801), the pharmacist-physician who recommended the use of arsenic solution for the treatment of agues and fevers.<sup>522</sup> With a substance as poisonous as

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<sup>522</sup> Fowler, T., Medical Reports of the Effects of Arsenic in the Cure of Agues, Remitting Fevers and Periodic Headachs, London, 1786.

arsenic a careful control over its administration was imperative. Fowler recommended the preparation of a solution by dissolving sufficient white arsenic (arsenic trioxide) in water with the aid of an alkali so that in the final preparation 64 grains were contained in one pound. Knowing that there were exactly 4 grains in each ounce, Fowler ascertained that  $\frac{1}{2}$  grain was contained in 80 'drops' and this enabled him to recommend doses in terms of the 'drop' as a unit, the number administered varying with the age of the patient.<sup>523</sup>

ii. Scientific Studies relating to Dose

A number of studies were carried out in the eighteenth century on the subject of dose. These may be broadly classified into two groups: first, those studies in which direct attempts were made to determine the doses of medicaments so as to improve general therapy, and, second, those studies in which dose was one of the factors involved in a planned experiment.

(a) Studies of therapeutic doses.

An early attempt to systematize the doses of

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<sup>523</sup> Ibid., pp. 79, 82, 85. A solution of Arsenic trioxide under the name Liquor Arsenicalis or Fowler's Solution of approximately the same strength was retained in the British Pharmacopoeia until 1953.

drugs in common use was made by the naval surgeon William Cockburn (1669-1739), who undertook this study as a means of demonstrating how the discoveries of science may be used to solve problems of practical therapeutics:

"And therefore I resolved to shew, how these excellent Discoveries [of Harvey and Sanctorius] might be applied in every part of Physick." 524

Unfortunately this desire to use the knowledge of great scientists did not induce him to apply their experimental methods.

Cockburn had observed a considerable variation in the effects of emetics and purges and he concluded that this was due to differences in the ages and physical condition, or constitution, of the patients. To account for this he drew attention to the then generally held belief that medicines act by first entering the blood, and he suggested that differences in doses were due to differences in the 'thickness' of the blood, this property of the blood varying with age and physique.<sup>525</sup>

In 1704 Cockburn dramatically challenged the physicians of Europe, through the medium of the

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524 Cockburn, W., The Nature and Cure of Fluxes, London, 3rd edition, 1724, p. 323.

525 Cockburn, W., Phil.Trans., 1704, 24, 2119; and 1708, 26, 48.

Philosophical Transactions (1704, 24, 1753), to seek a method for determining the doses of purges and emetics according to the age and condition of the patient. He later claimed with characteristic self-advertisement that Boerhaave had been unable to solve the problem, that others declared it impossible, and that he had published his own solution at the request of the Académie Royale des Sciences of Paris.<sup>526</sup> This solution was delivered in a paper written in Latin to the Royal Society in 1705 under the title: "The Solution of the Problem for determining the proper doses of purging and vomiting medicines, in every age of a man, in every constitution all over the world: which proposed in the Philosophical Transactions, March 1704." <sup>527</sup>

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<sup>526</sup> Cockburn, W., The Nature and Cure of Fluxes, London, London, 1724, p. 326.

<sup>527</sup> "Solutio Problematis de Purgantium et Emeticorum Medicamentum Dosibus determinandis in qua eunque Hominis Aetate, Temperamento, Temperamenti varietate per universum Terrarum orbem, ab ipso mense Martio proxime elapso, in Actis Philosophicis propositi." Phil.Trans. 1705, 24, 2119.  
The English translation of the title is the author's own as given in his The Nature and Cure of Fluxes, London, 1724.

In this Cockburn suggested that three factors were associated with the action of emetics and purges: one, the quantity of the blood; two, its thickness or degree of cohesion; and three, its velocity. For the first he postulated that the dose must be in a simple proportion to the quantity of blood. The other two factors he observed were related to each other and he put forward a proposition intended to take both into account. It was as follows:

"In two men, each having the same volume of blood, but with different thickness, then the dose of purgative or emetic medicines to bring about the same effect are in proportion to the square of the thickness."

This is a pharmacological extension of iatro-physics and the proof was based on the premise that the velocity of the blood in the vessels is inversely proportional to its 'thickness'. Cockburn argued as follows:

- i, if the velocity is constant then the dose will be proportional to the thickness;
- ii, if the thickness is constant then the dose is proportional to the reciprocal of the velocity; but

iii, if neither velocity or thickness are constant then the dose is in proportion to both thickness and reciprocal of velocity and it follows that the dose is in proportion to the 'duplicate proportion' or square of the thickness.

The proof of the proportion may be more clearly expressed as follows:

Let  $t$  = thickness of blood

$v$  = velocity of blood, which may be expressed in terms of the reciprocal of the thickness,

$$\text{i.e., } v = \frac{1}{t}$$

$d$  = dose for normal adult healthy constitution.

Then i,  $v$  constant: calculated dose =  $td$ , i.e., as thickness increases dose increases.

ii,  $t$  constant: calculated dose =  $d \times \frac{1}{v}$ ,  
i.e., as velocity of blood decreases owing to increased thickness so dose increases.

iii, if neither  $t$  or  $v$  constant, then

$$\begin{aligned} \text{calculated dose} &= d \times t \times \frac{1}{v} \\ &= d \times t \times \frac{1}{\frac{1}{t}} \\ &= d \times t^2 . \end{aligned}$$



This solution to the problem of dose was not well received by the physicians who on Cockburn's own admission regarded it merely as an ingenious speculation upon a hypothesis.<sup>528</sup> It had no practical application because there was no indication of how to measure the 'thickness'. Nevertheless some members of the Royal Society were impressed and four years later it was Sir Isaac Newton, then President of the Society, who persuaded Cockburn to publish a second paper on the subject. In this paper<sup>529</sup> he gave some practical application to his ideas by postulating that the volume of blood is proportional to age and that its 'thickness' corresponds to the constitution of the patient. He calculated doses to correspond to four ages and to three constitutions. The ages were:

- |    |                  |                  |                                    |
|----|------------------|------------------|------------------------------------|
| 1. | Man 16-20 years, | Weight 12 stone. | Normal or<br>empirical dose given. |
| 2. | 9 years          |                  | 3/4 normal dose                    |
| 3. | 6 years          |                  | 1/2 normal dose                    |
| 4. | 3 years          |                  | 1/4 normal dose.                   |

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<sup>528</sup> Cockburn, W., The Nature and Cure of Fluxes, London, 1724, pp. 326-7.

<sup>529</sup> Cockburn, W., Phil.Trans., 1708, 26, 46.

For each of these ages there were three possible healthy constitutions denoted 2, 3, and 4, where 3 represented the normal and 2 the most fluid blood. These constitutions corresponded to pulse-rates. The common or empirical dose for each age was to be given for the normal constitution and, therefore, is proportional to  $3^2$ . In order to calculate for other constitutions it is necessary to multiply the common dose by the square of the patient's constitution and divide by the square of the middle or normal constitution. Example: the accepted adult dose for Cassiae was given as  $\frac{480}{3}$  i or 480 grains; doses for other adult constitutions would be calculated as follows:

	<u>Const.</u>	<u>Common dose</u>	<u>Calculated dose</u>
	2		$480 \times \frac{2^2}{3^2} = 213 \text{ gr.}$
<u>Age</u> 16-20	3	480 grs.	= 480 gr.
	4		$480 \times \frac{4^2}{3^2} = 853\frac{1}{3} \text{ gr.}$

On this basis Cockburn drew up a table of doses for the whole range of emetic and purgative drugs then in common use (see Plate VII).

Many criticisms may be directed at this work. The most ~~prominent~~<sup>evk</sup> is that it is based entirely on the belief that the thickness or viscosity of the blood varies

TABLES,  
*Shewing the Doses of purging and vomiting Medicines  
 according to the Solution of D<sup>r</sup> COCKBURN'S Problem.*

	Medicines	Ages.	Doses					Medicines	Ages.	Constitutions.	Doses					Medicines	Ages.	Constitutions.	Doses			
			3.	2.	1.	Gr.					3.	2.	1.	Gr.					3.	2.	1.	Gr.
Medi- cines Dose 3i	Ca. sua	10	2	3	1	13 $\frac{1}{3}$	Common Dose 3i	Igaricus	10	10	2	0	1	6 $\frac{2}{3}$	Common Dose 3i	Refina ja	16	16	2	0	0	8 $\frac{2}{3}$
	Catholom		3	8	0	0		Aloe			3	1	0	0		lappa			3	0	1	0
	Diacar-		4	14	0	13 $\frac{1}{3}$		Carthamus			4	1	2	6 $\frac{2}{3}$		Extr rha-			4	0	1	15 $\frac{2}{3}$
	Elect leni-							Ebuli sem.								artari						
	trum	9	2	2	2	0		Cortex	9	9	2	0	1	0		Pl. de Her-	9	9	2	0	0	6 $\frac{2}{3}$
	Succus		3	6	0	0		Hermodac-			3	0	2	5		modacty			3	0	0	15 $\frac{2}{3}$
	radic. Frd		4	10	2	0		tyli.			4	1	1	0		lu 3ii			4	0	1	6 $\frac{2}{3}$
	Fr-							Mechoa-	6	6						pulv Cor-	6	6				
	maria	6	2	1	2	6 $\frac{2}{3}$		canna			2	0	0	13 $\frac{1}{3}$		nach 3ii			2	0	0	4 $\frac{1}{2}$
	Syrup de		3	4	0	0		Pil. Aggre-			3	0	1	10		Emet.	3	3	3	0	0	5 $\frac{2}{3}$
	Rhamno-		4	7	0	6 $\frac{2}{3}$		gatur	3	3	4	0	2	13 $\frac{1}{3}$		Gulla			4	0	0	8 $\frac{2}{3}$
	de Po-	3						Coch								vitroli						
	mus magis		2	0	2	13 $\frac{1}{3}$		major			2	0	0	6 $\frac{2}{3}$					2	0	0	2 $\frac{2}{3}$
	Rosar-		3	2	0	0		Fetida	3	3	3	0	0	15 $\frac{2}{3}$		Colocynthis	16	16	3	0	0	6 $\frac{2}{3}$
	cum Helleb-		4	3	1	13 $\frac{1}{3}$		fine 3ii			4	0	1	6 $\frac{2}{3}$		Euphorbium			4	0	0	10 $\frac{2}{3}$
	Jamarunda	10						bus								Esula Cor-						
	Sal cathar-		2	1	2	6 $\frac{2}{3}$		Pulv. Dux	10	10	2	0	0	13 $\frac{1}{3}$		tex	9	9	2	0	0	2
	tic amar		3	4	0	0		snaz			3	0	1	10		Elaterium			3	0	0	4 $\frac{1}{2}$
	Mura-		4	7	0	6 $\frac{2}{3}$		Rhal ar			4	0	2	13 $\frac{1}{3}$		Gum. Gutta			4	0	0	8 $\frac{2}{3}$
	ble							larum	3	3						Gran. simul	6	6				
Medi- cines Dose 3i	Alann. 3ii	3	2	0	2	13 $\frac{1}{3}$	Common Dose 3i	Soldanel-			2	0	0	6 $\frac{2}{3}$	Common Dose 3i	Scammom.	16	16	2	0	0	1 $\frac{1}{3}$
	Emetica		3	2	0	0		la			3	0	0	15 $\frac{2}{3}$		Tr. Alhand			3	0	0	3 $\frac{1}{3}$
	Vin eme-		4	3	1	13 $\frac{1}{3}$		Senna			4	0	1	6 $\frac{2}{3}$		Emet			4	0	0	5 $\frac{2}{3}$
	ticum,							Turbith								Crete Ru-	3	3	2	0	0	3 $\frac{2}{3}$
	feu Bened	10	2	1	2	6 $\frac{2}{3}$		Jalappa	10	10	2	0	0	13 $\frac{1}{3}$		landi			3	0	0	1 $\frac{1}{3}$
	Suc. Nari-		3	4	0	0		Juli ju-			3	0	1	10		Turbith mi-			4	0	0	2 $\frac{2}{3}$
	Senecio-		4	7	0	6 $\frac{2}{3}$		glandis			4	0	2	13 $\frac{1}{3}$		nerale	16	16				
	us							Lap. Lazu-	9	9						Emet						
	Confectio	9	2	1	1	0		li			2	0	0	10		H. A. tr-	9	9	2	0	0	1 $\frac{1}{3}$
	Flamech.		3	3	0	0		Arme-			3	0	1	2 $\frac{1}{2}$		y			3	0	0	3 $\frac{1}{3}$
	Elect. Car-		4	5	1	0		Opopanax	6	6	4	0	2	0		utr. 1 t			4	0	0	5 $\frac{2}{3}$
	ryocostin.							Pil. Coch								7k. ut	6	6				
	Diapha-	6	2	0	2	13 $\frac{1}{3}$		minor			2	0	0	6 $\frac{2}{3}$		7rt emet			2	0	0	2 $\frac{1}{4}$
	nicon		3	2	0	0		de Gut.	3	3	3	0	0	15 $\frac{2}{3}$		El. pne-			4	0	0	4 $\frac{1}{2}$
	6 succo		4	3	1	13 $\frac{1}{3}$		Gamandra			4	0	1	6 $\frac{2}{3}$		per 1	3	3				
	Rosarum							Rudu-								filur						
	Emet	3	2	0	1	6 $\frac{2}{3}$		Pul War-	3	3	2	0	0	3 $\frac{1}{3}$		rules			2	0	0	2 $\frac{1}{2}$
	Syrupus		3	1	0	0		vicensu			3	0	0	7 $\frac{1}{2}$					3	0	0	4 $\frac{1}{2}$
	emeticus		4	1	2	6 $\frac{2}{3}$		Cappereum			4	0	0	13 $\frac{1}{3}$					4	0	0	1
								Emet	3	3												
		3	2	0	1	6 $\frac{2}{3}$		Rad Ip-			2	0	0	3 $\frac{1}{3}$					2	0	0	2 $\frac{1}{2}$
			3	1	0	0		cacuana			3	0	0	7 $\frac{1}{2}$					3	0	0	4 $\frac{1}{2}$
			4	1	2	6 $\frac{2}{3}$					4	0	0	13 $\frac{1}{3}$					4	0	0	1

in disease and health. Also, because the work lacked an experimental basis, the calculated doses had to be based on the empirical doses then in common use and therefore it could not succeed in advancing a knowledge of true dose. In spite of these failures Cockburn's studies are not without some merit. He had observed, for example, that the effects of a medicine varied with the form in which it was administered: an infusion produced its effects sooner than a powder, a powder sooner than a 'bolus' (a soft mass) and a bolus sooner than a pill (a hard mass). He explained these differences by saying that, since medicines must first enter the blood before they can act, it follows that the rate of action is related to the rate at which they are dissolved and absorbed. Thus he had noted that the dose-effect relationship depends upon the nature and the absorption of the drug, as well as upon the quantity administered. It has been said of Cockburn<sup>530</sup> that, like his contemporaries, he wrote on theories unsupported by evidence and that he was content to neglect experiment provided his opinions were accepted and his reputation enhanced. His papers on doses could be used in support of this opinion. At the same time, however, they do

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<sup>530</sup> Keevil, J.J., Medicine and the Navy, 1200-1900, London, 1958, Vol. ii, p. 387.

represent an attempt to standardize and to adjust the dose according to the age and physical condition of the patient, a vital consideration when one is using powerful emetics and purgatives.

Stephen Hales adopted mechanical theories similar to those of Cockburn's to explain the results of his experiments with medicinal liquors and his work in turn led to another attempt to investigate doses by application of purely mechanical reasoning. This was the work of Charles Balguy (1708-1767), a physician of Peterborough, who outlined the problem in the following words:

" .... there is nothing in Practice more material, and yet less understood, than the Art of adjusting .. Doses so nicely to the Case in hand, and to the Age, Size and Strength of the Person, that he shall receive the most speedy and certain Relief these Medicines are capable of giving, without the Hazard of burthening Nature, and overdoing the Constitution." <sup>531</sup>

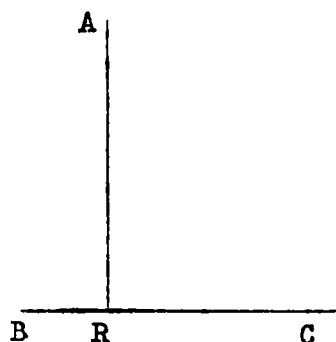
He began by modifying Cockburn's scheme on the basis that only part of the drug administered entered the blood.<sup>532</sup>

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<sup>531</sup> Balguy, C., Medical Essays and Observations, Edinburgh, 1737, 4, 33.

<sup>532</sup> Ibid., p. 34 et seq.

He later turned his attention to astringent medicines and suggested that their doses be determined by measurement of what he called their 'proportional force'. This arose from a suggestion of Stephen Hales which was that long animal fibres moistened with astringent medicines will contract. To measure small degrees of contraction Balguy proposed that the fibre AR be attached to a lever BC which is fixed at the point B. A contraction of the fibre of  $1/100$  inch will cause the lever to rise  $1/10$  inch at C.<sup>533</sup>



Another class of medicines that Balguy proposed to study were those that either attenuate or thicken the blood. The method proposed was as follows: a quantity of the medicine in solution was to be placed in a phial and kept at body-temperature. Fresh blood from a vein was then to be poured on top of this solution to fill the phial,

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<sup>533</sup> Balguy, C., Medical Essays and Observations,

Edinburgh, 1742,5,,83.

which was then closed with a stopper pierced with a glass capillary tube. "It is easy to see" wrote Balguy, "that the least Rarefaction will be perceivable by the Blood's ascending in the Tube." <sup>534</sup> He subsequently communicated this idea to Hales, who suggested that measuring the change in the specific gravity of the blood would also contribute to a knowledge of the attenuating properties of medicines. As far as is known these methods were not pursued further. Balguy did propose that the methods he had described should be used to determine the doses of astringent and attentuating drugs, but he went only as far as to call for assistance in the task, which he described as being "too great an Undertaking for one Person, who cannot pretend to lay out his Time wholly on such Amusements."

These mechanical theories gave the satisfaction of suggesting that the effects of medicines could be easily measured, with the result that Hales and Balguy thought it possible to relate dose directly to the density of the blood or to the tension of a fibre. The failure of such simple measurements for the determination of doses

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<sup>534</sup> Balguy, C., Medical Essays and Observations,

Edinburgh, 1742, 5, p. 85.

and effects can be illustrated by the experiments carried out by William Alexander of Edinburgh ~~of Edinburgh~~ to which reference has already been made. His method was simply that of self-administration of the drug in ascending order of dose, while attempting an objective measurement of the effect by measuring the pulse-rate and by observing changes in the body-temperature by a thermometer placed in the pit of the stomach. He began with Castor, a reputed antispasmodic and cordial restorative, taking from 10 to 120 grains of the substance.<sup>535</sup> The only effects he observed were symptoms of indigestion and he concluded correctly that the substance is valueless as a cardiac medicine. He reached similar conclusions regarding the medicinal properties of Saffron. Experiments with Nitre (potassium nitrate) were more positive. He took large doses and after 60 grains he experienced a diminution of the pulse and after 90 grains giddiness and

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<sup>535</sup> Alexander, W., Experimental Essays: II On the Doses and Effects of Medicines, London, 1768, p. p. 78, et seq. Note: Castor is an animal secretion and is found in two sacs situated near the tail of the beaver. It was used as a medicine by the Greeks. Its last official appearance in Britain was in the B.P. 1867, where it is described as the dried preputial follicles and their secretion, obtained from the Beaver, Castor Fiber, Linn.



irregularity of the pulse. Alexander attributed these symptoms (which are of cardiac depression characteristic of large doses of the salt) to a retardation of the velocity of the circulation and this prompted him to recommend the salt for high blood-pressure, "where the momentum of the blood is so great ... that the vessels are in danger of being ruptured". It is indeed fortunate that he recommended also a degree of caution, for his doses of 60 to 90 grains are far too great for safety.

His experiences with Castor, Nitre and later with Camphor, when he poisoned himself,<sup>536</sup> illustrate the weakness of his method. This method of self-medication with attempts at the measurement of one or two body changes will only suggest that a drug is inert or, more positively, discover toxic effects. It could not to any fine degree advance a knowledge of dose and effect; first, because of a lack of adequate controls, and, second, because in these circumstances accurate observation is limited. He found later, for example, in his work on diuretics<sup>537</sup> that the volume of urine excreted following

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<sup>536</sup> See page 314.

<sup>537</sup> Alexander, W., Experimental Essays, III On Diuretics and Sudorifics, London, 1768, p. 149, et seq.

the self-administration of a known volume of diuretic fluid was too variable to enable him to reach a conclusion. Excretion of course depends upon the ambient temperature and exercise; and, since Alexander was both experimenter and subject, these factors were difficult to control.

The researches of Cockburn, Balguy and Alexander are interesting because they illustrate a desire for a scientific determination of therapeutic doses. In the last analysis, however, in the eighteenth century as in previous times the only methods that yielded any results at all were the purely empirical studies conducted in the course of general practice; and if during this period Stoerk and Withering were more successful in their evaluation of dose and effects than their predecessors, it was simply due to greater precision in their clinical approach and to their application of the scientific principles of standardization, uniformity of administration, adequate controls and careful unbiased observations.

(b) The application of dose in experimental studies of drugs and poisons.

The majority of those who carried our experiments on animals with drugs and poisons in the 18th century recorded the weight or the volume of the substance administered. With poisons or supposed poisons the object in

most cases was actually to determine the toxic dose. In other cases, however, dose was used simply as one of the factors that had to be observed in a controlled experiment.

Madden recorded the large toxic doses of cherry-laurel water that he administered to dogs and later Browne Langrish recorded studies of both toxic and non-toxic doses of the same substances. Alston administered known quantities of opium solution to frogs and he was aware that the varied effects he observed were dependent upon the dose administered. Kaau Boerhaave reported the effects of opium upon the intestines of a dog after the administration of 3 and 6 grains doses. Robert Whytt was also careful to record the quantity of opium he used in each of his experiments and similarly Alexander Monroe, who recorded whenever necessary the volume administered. Monroe, like Alston before him and Wilson Philip later on, recorded his doses in terms of the 'drop', a most unsatisfactory unit of measure, since its size depended on the concentration of the solution and on the vehicle or solvent used. Other notable experimentors were Haller and his pupils, Sproegel and Zimmerman, all of whom administered measured quantities of poisons to experimental animals and observed the effects following varied doses of opium. Finally Fontana had a full appreciation of the dose-effect

relationship and, as we have seen, he went to some lengths to determine the minimum toxic doses of viper venom and the Ticunas arrow-poison. It is interesting to note that it is by means of dose that Fontana differentiated between venoms and vegetable poisons and the 'poisons' that cause smallpox and canine madness (hydrophobia).<sup>538</sup> The effects of the former were entirely dependent on the quantity administered and, therefore, on the amount circulating in the blood. The effects of smallpox and hydrophobia were, by contrast, caused by a poison that actually increased in the body.

In the eighteenth century two of the three factors necessary for an investigation of dose-effect relationships were established. The importance of a standardized preparation was appreciated and dose was accepted as an essential factor in experiments with drugs and poisons. But, although the presence of an active constituent was suspected in many cases, little progress in their extraction had been achieved by the end of the century. A number of drugs contain more than one active principle and the strength of a crude drug sometimes depends upon the time of its collection or the manner of

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<sup>538</sup> Fontana, F., Traité, Florence, 1781, Vol. II, p. 83.

its preparation (note, for example, the loss of hydrocyanic acid from some preparations of Cherry-laurel water). It is because of these factors that only the separation of the active constituent could lead to a final evaluation of a true dose-effect relationship and so to a full knowledge of the pharmacodynamic action of the drug. Work to achieve this separation, although carried out during the eighteenth century, did not reach its fruition until the early years of the nineteenth.

iii. Development of Knowledge concerning the Active Constituents of Drugs and Poisons.

In early European medicine it was generally believed that the medicinal virtue resided in the whole preparation which was carefully compounded of a number of simples. It was not until late in the seventeenth century that it became generally acknowledged that this activity could be attributed to but one or two of the ingredients. This was eventually to lead to a simplification of pharmaceutical formulae. One of the more immediate results was the publication of lists in which the weight of the active ingredient, where known, was related to the dose of the whole preparation. An example is to be found in the Pharmacopoeia Bateana (London, 1688),

where, in the Tabula posologica, the doses of the preparation and constituent purgatives are shown side by side, e.g.

Decoct. Senae Gereon	} iii	{ Senae } ii	
		{ Polypod }	ss
Diaprun.Solut,	{ viiss - Scammon. }		i
Diascordii	{ v grs.xii - Opii gr. i		
Pil.de Eupator maj.	{ i	{ Rhubarb grs. vii	
		{ Aloes }	ss 539

This became common practice in the eighteenth century and similar lists occur in successive editions of the Pharmacopoeia Londinensis.

Coincident with this development was the realization that the activity might possibly reside in a particular part or fraction of the crude drug itself. Following this trend of thought the French academicians attempted to discover the 'virtues' of vegetable drugs by means of chemical analysis. The early attempts of analysis by such methods as destructive distillation failed,<sup>540</sup>

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<sup>539</sup> The Pharmacopoeia Bateana was a collection of prescriptions used by George Bate (1608-1669), physician in turn to Charles I, Oliver Cromwell and Charles II.

<sup>540</sup> See p. 37.

but the gentler methods of extraction with one or more solvents proved to be more successful although they were a long way from the identification of the active principles. Simon Boulduc (d. 1729)<sup>541</sup> submitted the grey (Cartagena) and brown (Rio) ipecachuanna to a double extraction, first with water and then with alcohol. When the extracts were administered to patients, it was found that the separated resin had a more violent action than the root itself, while the saline fraction was only a gentle purgative. A similar process was carried out on Jalap root. Here again the resin exhibited a violent action, and Boulduc concluded that such extraction was contra-indicated since it would appear that Nature had endowed the natural drugs with a corrective to mitigate their more violent effects. He says of Jalap, for example, that the saline particles "in opening the resinous parts, dissolving and accelerating their distribution hinder them from adhering to and inflaming the parts they come into contact with".<sup>542</sup>

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<sup>541</sup> Boulduc, Mém.Acad.R.Sci., 1700 (pub. 1703), pp. 1, 76.

<sup>542</sup> Ibid., 1701 (pub. 1704), pp. 106-109:

"... les parties salines étendent les parties resineuses, les dissolvent, en accélèrent la distribution, & empêchent par là, que les parties resineuses n'adhèrent & n'enflâment les parties" (p.109).

The process of extraction became generally recognized as the most suitable method for increasing a particular action of a drug. In 1720 Patrick Blair<sup>543</sup> (d. ca. 1728) reported that:

"Senna will impart its purgative quality to water and ale, having its saline particles more disengaged: but the purgative virtue of Jalap, consisting in its resin, requires wine or brandy for the menstruum or dissolvent".

He concluded that:

".... a most proper way to find out the virtue of plants, is to have recourse to the proper menstruums".

Numerous attempts were made in the eighteenth century to extract the active constituent of drugs and some of these were associated with pharmacological experiments to test the different fractions. Early in the century Caspar Neumann<sup>544</sup> subjected opium to the process of extraction with alcohol (rectified spirit of wine) and water. He obtained alcohol-soluble resins, water-soluble 'gums' and saline matter. He

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<sup>543</sup> Blair, P., Phil.Trans., 1720, 31, 30.

<sup>544</sup> See p. 160. :



administered the resin to dogs and from the result he concluded that the resin was either the active principle itself or the seat of the active constituent of whole opium. Thus he ascribed the activity of the drug to a fraction of its whole. Later Alexander Monro secundus, in support of his theory of absorption, suggested that the active principle of opium was a minute portion of the whole.<sup>545</sup>

It became generally recognized that opium consisted of a mixture of a resin and a 'gum', and an application of this idea is to be found in John Leigh's experimental study of opium. Leigh began by dividing the drug into its constituent parts by macerating with water to obtain the gum and with alcohol to extract the resin. From one ounce of crude opium he obtained } ii } i of resin, } iii, 50 grs. of gum and } i 6 grs. of residue described in his work as 'Feculent matter'.<sup>546</sup>

The work that Leigh carried out with these extracts is of interest for two reasons. First, he demonstrated that the water-extractive or 'gum', which we

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<sup>545</sup> see p. 195. .

<sup>546</sup> Leigh, J., An Experimental Inquiry into the Properties of Opium, Edinburgh, 1786, pp. 29-34.

now know to have contained morphine, had narcotic properties and, second, as a result of the experiments, he attempted to produce a 'pure' opium consisting only of the active resin and gum. The prevailing opinion was that only the resin was active, but Leigh discovered that four grains of the water-extractive given to a young man caused drowsiness, depression, nausea and finally frightful dreams. Similar results were experienced when five grains of the material were given to a woman. He concluded that both resin and gum were active and that the effects of the resin were more dangerous. To produce a purified opium consisting only of the active constituents and free of the 'feculent matter', he suggested that the crude drug should be heated with a mixture of alcohol and water for a prolonged period and then filtered and evaporated to the consistence of an extract:

"When we have an opium in this pure state, the physician, who is acquainted with its operation, will be enabled to form, as to its effects, a true opinion, and will also have some prospect of certainty in the dose which he may administer."<sup>547</sup>

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<sup>547</sup> Leigh, J., An Experimental Inquiry into the Properties of Opium, Edinburgh, 1786, p. 54.

Leigh's work with opium was characteristic of a number of similar experiments at this period that never went beyond extracting water-soluble 'gums' and alcohol-soluble 'resins'. Another example is the work of Benjamin Smith Barton (1766-1816) of Philadelphia, whose thesis on the hyoscyamus niger won the Harveian prize for 1787. It was noted at the time that he had taken great pains to extract the constituents of the hyoscyamus, i.e., the gummy and resinous extractives.<sup>548</sup>

In the second half of the eighteenth century it was generally agreed that the activity of a drug or poison resided in a part of the whole. The separation of resins, gums and salts, was the first step in the isolation of the active constituents. The further progress in the field lay with developments in chemistry and in particular with the analysis of plant and animal materials and the isolation of natural organic compounds. Although the full history of these developments, in which plants having a medicinal or poisonous nature were to be subjects of particular interest, is outside the scope of the present study, the isolation of certain active constituents is of special interest to posology

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<sup>548</sup> Medical Commentaries, Edinburgh, 1787, 2, 400.

and pharmacology, in particular with regard to hydrocyanic acid and the medical alkaloids, morphine, emetine and strychnine.

One of the most elaborate, careful and unsuccessful searches for an active constituent was carried out by Fontana in 1781 in his attempts to isolate or concentrate the active constituent of the cherry-laurel leaf. The toxic substance, which Fontana knew to exist but failed to discover, was synthesized soon after by the apothecary-chemist Carl Wilhelm Scheele (1742-1786). In the course of his experiments<sup>549</sup> with Prussian blue, Scheele heated yellow prussiate of potash with sulphuric acid and so obtained what was later called hydrocyanic acid. Scheele was unaware that this substance, which he called 'colouring principle' (and which Guyton de Morveau named Prussic acid),<sup>550</sup> was the toxic constituent of certain plants; indeed he was unaware of its toxicity and describes it as having a not unpleasant smell and a slightly sweet taste, heating the mouth, and a tendency to provoke

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<sup>549</sup> Scheele, C.W., Kongl. Vetenskaps Academiens Nya Handlingar, 1782, 3, 264-275; 1783, 4, 33-43.

<sup>550</sup> See Hoefer, F., Histoire de la Chimie, Paris, 1869, vol.ii, 468. The name acide prussique was given in Vol. I of Guyton de Morveau's Encyclopédie Méthodique (1786) and it soon came into general use in Britain and France.

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coughing.<sup>551</sup> It was fortunate for Scheele and for the science of chemistry that he had not obtained the acid in a more concentrated form!

The discovery that cherry-laurel leaves contained prussic acid was reported in 1802 by the German apothecary and 'Medicinal Assessor' in Berlin, Johann Christian Karl Schrader (1762-1826). He observed a resemblance in odour between the acid (Blausäure) and the distilled products of bitter almonds, peach leaves and cherry-laurel leaves.<sup>552</sup> To prove the presence of the acid in these products he treated the distillate with lime, added iron sulphate and acidified, whereupon he obtained Prussian blue. Having confirmed the presence of the acid in the leaves, he put small birds into containers with the acid. The manner of their death convinced him that the acid was the toxic principle in cherry laurel and bitter almonds.<sup>553</sup>

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<sup>551</sup> See Collected Papers of C.W. Scheele, Trans. by L. Dobbin, London, 1931, p. 247.

<sup>552</sup> Schrader, J.C.C., Journal de Physique, de Chimie, et Histoire Naturelle, 1802, 56, 224.

<sup>553</sup> Later the acid was isolated from other plant sources. In 1811 another Berlin apothecary, G.W. Bergeman discovered the acid in the bark of the prunus padus

The discovery of hydrocyanic acid in cherry-laurel water had no immediate therapeutic significance, because this preparation, owing to its toxic properties, was not generally used in medicine. Schrader demonstrated that the acid was the toxic principle, and three years later Carl Friedrich Emmert (d. 1834), experimenting on dogs, proved it to be a dangerous poison.<sup>554</sup> It is all the more surprising, therefore, to find that within a short time the acid was introduced into therapy and, because of its toxicity, its standardization and dose became matters of interest and importance.

Hydrocyanic acid was first introduced into medicine in Italy by followers of Brunonism. Siro Borda (1761-1824), Professor at Pavia, had begun to use cherry-laurel water after the study of the substance by Fontana and, after Schrader's discovery, he recommended the pure acid for treatment of 'sthenic' diseases, i.e. diseases of high excitement. This was recorded by

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or bird-cherry tree. A distillate of the bark was already known to be fatal to dogs, (Ann. Chim., 1812, 83, 215 ).

<sup>554</sup> Emmert, C.F., Dissertatio inauguralis medica de venenatis Acidi Borussici in animalia effectibus, Praes. C.F. Kielmeyer, Tübingae, 1805.

Luigi Brugnatelli (1761-1818), who described it as an anti-excitant and an anthelmintic.<sup>555</sup> Rasori also recommended the use of the drug for sthenic diseases and Velerino Luigi Brera (1772-1840) in 1809 administered it in cases of pneumonia.<sup>556</sup> The acid was introduced into French medicine by François Magendie (1783-1855) and into England by Augusto Bozzi Granville (1783-1872).<sup>557</sup>

Magendie's paper was perhaps the most important and significant contribution on the subject of the

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555 Brugnatelli, L.V., Farmacopea Generale, Napoli, 1808, vol. iii, p. 123.

556 See Granville, A.B., An Historical and Practical Treatise on the Internal Use of the Hydro-Cyanic (Prussic) Acid, in pulmonary consumption and other diseases, London, 2nd ed., 1820, p. 106.

557 Granville had studied in Italy and he published his first paper on the hydrocyanic acid in 1815 in the London Medical Repository (1815, iv, 177). Little notice was taken of this paper and in 1818 after a visit to Paris he decided to publish a translation of Magendie's memoir on the subject (Journal of Science, 1818, 4, 347). A year later Granville published a short treatise on the subject of the therapeutic uses of the acid; this increased in size in the second edition (1820) from 100 pages to 418 pages (see Bibliography).

use of prussic acid in therapy. The memoir appeared in 1817 under the title "Mémoire sur l'emploi de l'acide prussique dans le traitement de plusieurs maladies de poitrine, et particulièrement dans la phthisie pulmonaire".<sup>558</sup> In it Magendie reported the use of the acid in a number of cases of pulmonary disease and recommended it as a cure for phthisis and as a sedative to reduce coughing. It was largely as a result of this paper that prussic acid was established in the official materia medica, where it was retained until comparatively recently.<sup>559</sup>

Magendie, in his clinical studies, had used the Scheele's acid which was then the common form. This product, however, presented a problem for those who would use it in therapeutics. This was because it was not properly standardized, its strength was variable and, therefore, the dose was subject to some variation. In an attempt to improve this Magendie turned to the purer form of the acid prepared by Gay-Lussac, who decomposed prussiate of mercury with hydrochloric acid.<sup>560</sup> In an

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<sup>558</sup> Magendie, F., Ann.Chim.Phys., 1817, 6, 347.

<sup>559</sup> Ac.hydrocyan.dil. was not deleted from the British Pharmacopoeia until 1948.

<sup>560</sup> Gay-Lussac, Ann.Chim., 1811, 77, 128.



experiment to discover the action of the Gay-Lussac acid, Magendie dipped a rod into it and then plunged the rod down the throat of a dog. The animal died instantly. Immediate death also occurred when one drop of the acid, diluted with four drops of alcohol, was injected into the jugular vein of a dog.<sup>561</sup> These experiments demonstrated the purity and extreme toxicity of the acid and Magendie realized that it was essential, if this product was to be used in medicine, that a standard preparation must be used so that dosage could be estimated. In his Formulaire pour la Préparation et l'Emploi de Nouveaux Médicaments (first published in 1821), he recommended that the acid be used in medicine and the dose based on a preparation which he called Medicinal prussic acid, consisting of one part of the pure acid diluted with six times its own volume of distilled water.

The discovery of the active constituent of cherry-laurel leaves proved to be a matter of identification. The acid was first prepared in the laboratory by Scheele and subsequently identified as the active principle of cherry laurel, bitter almond and other substances. With the alkaloids the situation was somewhat different.

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<sup>561</sup> Magendie, F., Ann.Chim.Phys., 1817, 6, 349.

They were discovered following their isolation from the crude materials and their supply for medicinal purposes, unlike the hydrocyanic acid, depended upon an extraction and purification from the parent drugs.

The first important development was with opium, the active constituents of which had been the subject for speculation over a number of years. In 1803 Charles Derosne (d. 1846)<sup>562</sup> obtained a crystalline substance (probably narcotine)<sup>563</sup> from an alkaline aqueous extract of opium, which he called 'salt of opium'. Séquin (1765-1835) described the isolation of morphine in 1804, but his work was not published for many years<sup>564</sup> and the credit for the discovery of this alkaloid, the first to be isolated in a pure state, is usually attributed to the Apotheker, Friedrich Wilhelm Adau Sertürner (1783-1814). In his first communication in 1805,<sup>565</sup> he described the acid in opium (opiumsäure, meconic acid). A year later<sup>566</sup> he announced the isolation from the drug

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<sup>562</sup> Derosne, C., Ann.Chim., 1803, 45, 257 et seq.

<sup>563</sup> Sertürner believed Derosne's product to be a morphine salt but Pelletier suggested it to be narcotine (see Ann.Chim.Phys., 1817, 5, 21; 1832, 50, 242).

<sup>564</sup> Ann.Chim., 1814, 92, 225.

<sup>565</sup> Sertürner, F.W.A., Journal de Pharmacie (Trommsdorff's), 1805, 13, 234, 236.

<sup>566</sup> Ibid., 1806, 14, 47 et seq.

of a narcotic principle : which he called principium somniferum. Little attention was paid to these early papers but immediate interest was aroused in 1817 when he again called attention to this principle, now called morphium, and described its basic properties.<sup>567</sup> His findings were confirmed within a year by another pharmacist,<sup>568</sup> Pierre-Jean Robiquet (1780-1840), who also, by exhaustive ether-extraction, isolated from opium another organic base, which was given the name narcotine.<sup>569</sup>

The discovery that these constituents were plant 'alkalies' or bases was the key to further progress in this field. In the period, after the republication of Sertürner's classic research, many new active bases were isolated from vegetable drugs and poisons. In 1817 Magendie and Pierre Joseph Pelletier (1788-1842) published a memoir on ipecahuanna, showing that the emetic properties were due to a constituent which Pelletier called emetine.<sup>570</sup> A year later Pelletier and Joseph-Bienaimé

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<sup>567</sup> Sertürner, F.W.A., Ann.der Physik (Gilbert's), 1817, 55, 56.

<sup>568</sup> Note. The majority of chemists associated with this early work on the isolation of alkaloids were pharmacists. They include Sertürner, Dorosne, Pelletier, Caventou, Robiquet, Meissner and Merk. See Dann, G.E., Praktische Apotheker als Begründer der alkaloidchemie Farm.Glas., 1955, 11, 317.

Caventou (1795-1877) isolated strychnine from nux vomica<sup>571</sup> and in 1819 they isolated brucine from the inner bark of the False Angustura bark.<sup>572</sup> The greatest contribution to medicine by these two great French chemists occurred in 1820 when they isolated quinine from cinchona bark.<sup>573</sup>

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- 569 Robiquet, P.J., Ann.Chim.Phys., 1817, 5, 275.
- 570 Magendie & Pelletier, Journ.de Pharmacie, 1817, 3, 145.
- 571 Pelletier & Caventou, Ann.Chim.Phys., 1819, 10, 142.
- 572 Pelletier & Caventou, Ann.Chim.Phys., 1819, 12, 113.  
Note. The False Angustura Bark was believed by the authors to be the bark of the Brucea Antidysenterica hence the name Brucine. (See Christison, R., Treatise on Poisons, Edinburgh, 1845, 4th ed., p.905).
- 573 Pelletier & Caventou, Journ.de Pharmacie, 1821, 7, 49. Note. A crystalline product had been obtained from cinchona bark by B. A. Gomes (1769-1824) about 1810. He called this product Cinchonin, the name which had been given to the (then unknown) active principle of the bark by A. Duncan in 1803. In 1820 Pelletier and Caventou showed that the Cinchonin was in fact a mixture of two alkaloids cinchonine and quinine.  
See Mem.da Acad.Real.das Sciencias de Lisboa, 1812, iii, 202 et seq. Edinb. med. surg. J., 1811, vii, 420; J. of Natural Philosophy, Chemistry, and the Arts (Nicholson's Journal), 1803, vi, 228.

The work in the isolation of active constituents was accompanied by experiments to determine the effects and the doses of the newly isolated substances. The examples of morphine, narcotine, emetine and strychnine may be given to illustrate this aspect of the work.

Morphine. Sertürner in his early work<sup>574</sup> reported experiments with the opium extractives on dogs. In one he reported that he dissolved 6 grains of der reinen Krystalle in alcohol mixed with sugar solution and gave it to a small dog. This dose proved to be too strong and so he dissolved 12 grains of the substance and then administered 1/24th of this solution, i.e., equivalent to 1/2 grain of the extract. He then doubled the dose at regular intervals, administering the whole over 6 hours. He was able by this method to observe a steady onset of symptoms from sleepiness to convulsions and finally death. Later<sup>575</sup> he made experiments upon himself and on others (young persons, none of them, according to the author, over seventeen years of age). In these experiments

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<sup>574</sup> Sertürner, W., Journal de Pharmacie (Trommsdorff's), 1805, 14, 77.

<sup>575</sup> Sertürner, W., Ann. der Physik (Gilbert's), 1817, 55, 68 et seq.

$\frac{1}{2}$  grain doses of morphine were given at regular intervals and it was observed that an initial excitation was followed by weakness, numbness and other symptoms of narcosis.

Shortly after this work was published, further experiments were carried out by Magendie and the Spanish-born toxicologist Mathieu Joseph Bonaventure Orfila (1787-1853).<sup>576</sup>

Orfila made some experiments with dogs using different acid salts of morphine. He reported the acetate to be the most powerful. Magendie gave the salts to human patients and reported that  $\frac{1}{4}$  grain of the acetate allayed pain and procured sleep.

Narcotine. Dorosne<sup>577</sup> made some experiments with his sel d'opium or narcotine, which in all probability contained some morphine. He gave the substance to dogs in doses ranging from four decigrammes to a gramme. The results resembled the effects produced by large doses of crude opium. Later, Magendie<sup>578</sup> made experiments with this substance but the results were confusing and, although he included the alkaloid in his Formulaire, he did not

<sup>576</sup> Orfila, Magendie, Nouveau Journal de Medicine, 1818, 1, 3, 23.

Orfila, M.J.B., Ann.Chim.Phys., 1817, 5, 288.

<sup>577</sup> Dorosne, Ann.Chim., 1803, 5, 281.

<sup>578</sup> Magendie, F., J.de physiol.expér., 1821, I, 34.

consider that sufficient was known about it for it to be offered as a medicine.

Emetine. The paper in which Magendie and Pelletier described the isolation of emetine was divided into two parts: Partie chimique and Partie physiologique et médicale.<sup>579</sup>

In the latter they describe experiments with animals and report observations made on human subjects. They found that a dose from  $\frac{1}{2}$  to 2 grains of emetine given to dogs and cats causes vomiting.<sup>580</sup> Later in the Formulaire Magendie notes that a purer form of emetine will kill a dog in a dose of two grains.

Quinine. When Pelletier and Caventou isolated quinine, they sent a sample to Magendie who made a simple experiment to determine its toxicity. He reported that a single dose of 10 grains in the form either of the sulphate or acetate could be injected into the vein of a dog without ill-effects.<sup>581</sup>

Strychnine. Pelletier and Caventou in their paper on the isolation of strychnine<sup>582</sup> reported experiments carried

579 Magendie and Pelletier, Journal de Pharmacie, 1817, 3, 145.

580 Ibid., p. 159.

581 Magendie F., Journal de Pharmacie, 1821, vii, 138.

582 Pelletier & Caventou, Ann.Chim.Phys., 1819, 10, 171, et seq.

out to determine the toxicity of the substance. Under the title Expériences physiologiques, they reported that  $\frac{1}{2}$  grain of strychnine isolated from the St. Ignatius's Bean (Ignatia amara, L.) was blown (fut insoufflé) into the mouth of a rabbit. Convulsions occurred within two minutes and these were followed by tetanus. The same dose was then inserted into a wound on the back of a rabbit. Symptoms of tetanus began after one minute and the animal died after three and a half minutes. The experiments were repeated, with the same results, using strychnine isolated from the nux-vomica seed. Similar work was carried out with the nitrate and hydrochloride salts of the alkaloid.

The effects of strychnine were already well known when it was isolated from its crude sources. In 1809 Magendie and Raffeneau Delille (1778-1850) examined the effects of extracts of nux vomica, St. Ignatius's Bean and the Javanese arrow-poison, the Upas tieute. They showed that all the extracts had the same effect, producing a form of convulsion which Magendie described as 'un vrai tétanos' and which he showed was due to a specific effect upon the spinal cord (vide infra). The isolation of strychnine discovered the active principle common to these extracts from different plant sources. Magendie recognized this and found that, although the strychnine produced



the same effects as the crude extracts, its action, dose for dose, was far greater. He found that  $\frac{1}{4}$  grain produced very pronounced effects upon a strong dog.<sup>583</sup>

The relationship between the alkaloid and its plant sources was indicated by Pelletier and Caventou in the name they gave it, strychnine from Strychnos. It is interesting to note that Magendie objected to this and suggested that it should be named tetanin, a name which, like morphine and emetine, indicated the pharmacological action of the substance.

These alkaloids were introduced into medicine by Magendie in the Formulaire. In the preface he called them the 'elements of medicines' and observed that the inability to isolate them had to that time retarded the progress of pharmacology. These new chemical remedies can be compared to the chemical remedies introduced into therapy in the seventeenth century. In both cases the substances were relatively pure and therefore easy to standardize in pharmaceutical preparations. They all possessed highly specific actions and were all potentially dangerous. Thus both groups possessed that purity and specific action that rendered it possible for a dose to

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<sup>583</sup> Magendie, F., Ann.Chim.Phys., 1819, 10, 176.

be determined. In the seventeenth century, however, methods for that determination had not been established and the new chemical substances were given in doses ranging from the ineffective to the near toxic. By the early nineteenth century the method of pharmacological experiment using animals had been established and, although Magendie indicates that a few still doubted the validity of such work, all the newly isolated substances were submitted to animal experiments and the results accepted as a basis for their use in human medicine. Thus Magendie in introducing these materials could report on their action and uses and specify doses. It will be seen from Table XV that these doses, reported in some cases but two to three years after the actual isolation of the alkaloid, are of an order that bear comparison with those used in our own time.

Table XV. Comparison of doses reported in the first edition of Magendie's Formulaire with official British Pharmacopoeias.

Alkaloid	Isolated	Formulaire 1821	B.P. 1867	B.P. 1958
Morphine	Séquin 1804 Sertürner <u>1805</u>	acetate: sulphate $\frac{1}{4}$ - 1 gr.	acetate hydro- chloride $\frac{1}{8}$ - $\frac{1}{2}$ gr.	sulphate $\frac{1}{8}$ - $\frac{1}{3}$ gr.
Strychnine	Pelletier and Caventou 1818	$\frac{1}{4}$ gr. reported toxic to dog & marked effect on humans. Therapeutic dose $\frac{1}{12}$ - $\frac{1}{8}$ gr.	$\frac{1}{30}$ - $\frac{1}{12}$ gr.	hydro- chloride $\frac{1}{30}$ - $\frac{1}{8}$ gr.
Emetine	Pelletier 1817	$\frac{1}{2}$ - 3 grs. cause vomiting in dogs and cats. 2 grs. cause vomiting in man. Emetic dose 4grs. 'Pure' emetine dose 2 grs. toxic to dog. Emetic dose 1 gr.	Not included	Hydro- chloride $\frac{1}{2}$ - 1 gr. by injection
Quinine	Pelletier and Caventou 1820	sulphate 1 - 10 grs. per diem.	sulphate 1 - 10 grs.	sulphate and hydro- chloride 5 - 10 grs.

5. KNOWLEDGE CONCERNING THE MODE OF ACTION OF DRUGS AND POISONS

In the early years of the nineteenth century the problem of the mode of action of drugs and poisons was centred on a controversy concerning the manner in which they exerted their general effects upon the body. Local effects were explained by the mechanical terms of irritation and corrosion, but these processes could not explain the narcotic effects of opium or the paralytic effects of the arrow poisons. These substances acted without causing any local reaction at the site of administration or, so far as could be seen, any mechanical effects upon the organ or organs that reacted so violently. When strychnine was shown to be the active constituent of a number of poisonous plants and when its dose and action on the spinal cord had been determined by animal experiments, there was still a controversy concerning the nature of the 'link' between the stomach or wound into which it had been administered and the distant organ of the body it affected.

In the seventeenth century it was generally accepted that a medicine was absorbed and the effects naturally followed.<sup>584</sup> The effects were believed to be on the

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<sup>584</sup> See p. 58.

solids and fluids of the body, and their particular actions were described in such terms as alterative, coagulant, dilata~~nt~~, stimulant and evacuant. Drugs that affected the consciousness and sensibility were believed to act upon the animal spirits in the nerves and brain. The violent action of a corrosive poison was attributed to a 'sympathy' existing between the stomach and other organs of the body.<sup>585</sup>

In the eighteenth century, attention was directed to the physiological problems associated with the manner in which a medicine or poison exerted its general effects upon the body. Contemporary medical theories together with certain researches and discoveries gave rise to two possible explanations: first, action through the agency of the nervous system either by some form of 'sympathetic action' or, more simply, by the substance affecting the nerves at the site of administration and the transmission of nervous stimuli to the organ affected; or, alternatively, action following the absorption of the substance into the circulation, the effects occurring either through direct action of the substance on the blood itself or by the substance

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<sup>585</sup> Willis, T., Pharmaceutice Rationalis, London, 1679,  
Part I, pp. 137-8.

being carried in the circulation to the organs of the body. The controversy concerning these alternative modes of action was principally directed towards the highly active substances the rapid effects of which were brought on by small, even minute, doses, e.g., the arrow-poisons, viper venom, opium, the alkaloids and hydrocyanic acid.

Early variations of the two modes of action were described by John Jones in 1701 in his study of opium.<sup>586</sup> He discussed the manner in which opium is said to exert its effects and noted that it might act directly on the blood or alternatively, as was more generally believed, on the brain, nerves and animal spirits. He gave a number of reasons in opposition to the idea that it acted as an alternative on the blood, following absorption from the stomach. The most interesting of these relates to the extensive effects of the drug compared to the size of the dose producing them. Jones observed that assuming a man has 20 pounds of blood (a high estimate, since it is nearer 12), one grain of opium dissolved in all this fluid bears a proportion to the whole of 1 to 153600. Giving these figures he asked how such a small weight

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<sup>586</sup> Jones, J., The Mysteries of Opium Reveal'd, London, 1701, pp. 37-92.

could be thought to affect such a large mass of blood.<sup>587</sup> This belief that a small dose greatly diluted in the blood could not produce the observed effects was to be one of the principal arguments of those who favoured the theory of direct action through the nerves.

The second explanation put forward by Jones, namely, that opium affected the nerves, brain and animal spirits, raised the problem of how the opium was transmitted to the brain from the stomach. Suggestions previously put forward included a direct effect upon the brain by vapours or fumes rising in some mysterious way from the stomach or a direct effect upon the stomach itself so that the brain acted in sympathy. A third, and more rational explanation, was that the opium was absorbed into the blood and actually carried in the circulation to the brain. Willis had put forward this view, and in his Pharmaceutice Rationalis he had written:

"Indeed, tis a sign that the Particles of Opium being eaten are presently carried into the Blood and swiftly pass thorow its Mass, because they suddenly, after the Medicine is taken, being carryed

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<sup>587</sup> Jones, J., The Mysteries of Opium Reveal'd, London, 1701, p. 94.

to the Encephalon, procure sleep and ease."<sup>588</sup>

Jones, who would appear to have set himself the task of opposing all that had been written concerning the action of opium, opposed this explanation by saying that such a route would involve the drug being carried first to the heart and lungs and that it should, therefore, interfere with the operation of those organs.<sup>589</sup>

Richard Mead, a contemporary of Jones, in the course of his work on poisons, contributed in turn to both theories of the mode of action. In the first edition (1702) of his A Mechanical Account of Poisons, he suggested that the 'acute points' in viper venom that had entered the blood through a wound attacked the globules of the blood and released the 'elastic' matter that they contained. This highly active substance then acted as a dispersing agent for the poison in the blood and thus the extensive effects that could result from very small doses were explained.<sup>590</sup> Opium, according to Mead affected the stomach, and this effect was heightened by its mixing

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<sup>588</sup> Willis, T., Pharmaceutice Rationalis, London, 1679, Part I, p. 143.

<sup>589</sup> Jones, J., The Mysteries of Opium Reveal'd, London, 1701, p. 71.

<sup>590</sup> Mead, R., Essays on Poisons, London, 1702, pp.14-15.



with the blood and distending the vessels of the brain.<sup>591</sup>

In the third edition (1745) of his work on poisons, although he continued to hold the same views concerning the action of opium, Mead made a radical change in his opinions concerning the action of other poisons. He now believed that all poisons, whether applied in a wound or swallowed, attack the nerves. He described this action in the following words:

"... the mischief does not stop at the part affected, but is carried farther, even through the whole body.

"This is done by the great activity of the nervous fluid, one part of which being infected immediately taints all the rest: and thus the whole system of nervous expansions is drawn into spasms and convulsions: and according to the different offices of the parts to which they belong, produce different symptoms." <sup>592</sup>

This change in opinion was due to the evidence of the rapidity of action of some of the poisons, particularly the snake poisons. Mead concluded that this action was

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<sup>591</sup> Mead, R., Essays on Poisons, London, 1702, p. 142.

<sup>592</sup> Mead, R., Essay on Poisons, London, 1745, 3rd ed., p. xxx.

far too quick to be explained by changes brought about in the course of the circulation.<sup>593</sup>

This problem of the rapidity of action had faced Willis, who noted that a patient becomes drowsy from opium almost immediately after the time required for it to dissolve in the stomach. He maintained however that "the Journey from the Ventricle [stomach] to the Head by the Blood is expeditious enough, and may be performed in a very little time."<sup>594</sup> Mead could not, however, believe that the blood could flow so quickly as to account for the swift action of certain poisons. As evidence he referred to the somewhat doubtful calculation of the English i~~3~~atro-mechanist James Keill (1673-1719), who had stated that the ratio of the velocity of the blood at the 40th branch of the aorta to that of the aorta itself is as 1 to 5233.<sup>595</sup>

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<sup>593</sup> Mead, R., Essay on Poisons, London, 1745, 3rd ed., p. xl.

<sup>594</sup> Willis, T., Pharmaceutice Rationalis, London, 1679, Pt. I, p. 138.

<sup>595</sup> Note. James Keill was an anatomist and mathematician, who studied by mathematical methods the physiological problems of secretion, blood-volume, blood-velocity, the force of the heart and muscular motion. Because of the methods that he used, his work has some historical interest, although the results themselves were subject to considerable errors, largely through

This argument, that the circulation could not be so swift as to account for the rapid action of certain poisons, was to become another of the principal arguments to be developed in favour of the theory of a direct action through the nerves.

Herman Boerhaave, whose teaching did so much to advance 18th century medicine, held the view that the effects of medicines followed absorption into the circulation. 'Topic' medicines, i.e., those having an effect upon a specific part of the body, e.g., cordials and cephalics, are first absorbed from the stomach and then carried to the affected part.<sup>596</sup> Other medicines enter the blood and are carried to affect the origins of the nerves, in the case of the emetics this brings about

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a want of experiment.

His studies in blood velocity first appeared in London in 1708 in his An Account of Animal Secretion, The Quantity of Blood in the Humane Body, and Muscular Motion. The figure given in the text appears on p. 75 in the second and enlarged edition of his work which appeared under the title Essays on Several Parts of the Animal Oeconomy (London, 1717). It should be noted that Mead, who quoted these figures, used as his reference the Latin edition, Tentamina Medico-Physica, London, 1718, p. 48.

<sup>596</sup> Boerhaave, H., Tractatus de Viribus Medicamentorum, Paris, 1723, pp. 321 et seq.

general muscular spasms which, together with spasms of the stomach, lead to an expulsion of its contents.<sup>597</sup> Boerhaave did not exclude the possibility of a direct action by the 'Particles' of medicine on the nerves at the site of application, and he gave as an example of this the effects of sternutatory drugs on the olfactory nerves. Where such action takes place, he suggested that the effects observed would vary according to the nerve affected.<sup>598</sup>

The works of Boerhaave and Mead indicate that, at the time they were writing, the theories of action through the circulation and direct action through the nerves were not mutually exclusive. It was not only accepted that some (the slower acting) drugs acted through the medium of the circulation while others acted directly upon the nerves, but also that some substances exerted their effects in both ways according to the circumstances. This is illustrated by Langrish's explanation of the action of Cherry-laurel water. He suggested that the mode of action is dependent upon the dose: small doses act on the blood following absorption, attenuating

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<sup>597</sup> Boerhaave, H., Tractatus de Viribus Medicamentorum, Paris, 1723, pp. 243 et seq.

<sup>598</sup> Ibid., p. 66.

and dividing it so that it assumes a bright florid colour. Large doses, however, which act rapidly, do so by a direct effect upon the nerves. He maintained that in such cases the rapid onset of convulsions and the loss of sensation were too quick to be explained by "that Pittance of Laurel Water, which may be imagined to enter the common Absorbent Vessels, which terminate in the Veins".<sup>599</sup> Since there was no evidence of an obstruction or inflammation of the blood vessels that would lead to a violent death, and since the onset of symptoms was too rapid to allow for some change in the constitution of the blood, it followed that the drug in large doses must act on the nerves. To explain further, Langrish suggested that the 'most subtle, sulphurous Particles' attract, fix and destroy the animal spirits whilst the grosser particles stimulate the nerves and cause convulsions.<sup>600</sup>

Langrish's explanations were based on the arguments of limited absorption and rapidity of action. Another factor governing the choice of explanation for the action of a substance was the nature of the symptoms

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<sup>599</sup> Langrish, B., Physical Experiments, London, 1746,  
p. 65.

<sup>600</sup> Ibid., p. 66.

observed, certain symptoms being attributed to an action through the blood, others, for example convulsions, to a direct action on the nerves. A classic illustration is Tissot's explanation of the two forms of ergotism. In one form the spasms and convulsions are due to the irritation of the nerves by the vitiated rye; the other form, characterized by gangrene, is said to be due to the ergot corrupting the blood.<sup>601</sup>

To summarize, we can say that there were three principal arguments put forward in support of the explanation of a direct effect upon the nerves. They were: the extent of the observed effects was out of proportion to the dose given or quantity believed to be absorbed in the time; their onset was rapid; and their nature suggested that they were of nervous origin. All three of these factors are characteristic of the highly active, non-corrosive poisons and narcotic drugs, which, as we have seen, were the principal subjects of experiment in the eighteenth century. It was to these substances that the theory of direct action through the nerves was specifically applied.

Charles Alston in his study of opium (1742)

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<sup>601</sup> Tissot, S.A., Phil.Trans., 1765, 55, 122.

stated that the anodyne and hypnotic power of the drug was not due to its action on the blood or on the brain, but to its effect on the nerves at the site of administration whence it affected the whole nervous system by

Consent.<sup>602</sup>

A similar belief was maintained by Kaau Boerhaave who suggested that the opium in the alimentary canal actually prevented the process of absorption.<sup>603</sup>

Robert Whytt also believed in the action of opium through the nerves and made a number of experiments the results of which, he suggested, proved the fact. He believed the drug affected the nerves at the site of administration, i.e., stomach or rectum, and through them affected the brain and spinal marrow by their "connexion and sympathy". He did not deny that opium was absorbed, but he considered the effects from this to be negligible. What effects there were, he believed to be due to the drug affecting the nerves on the inner side of the blood vessels. This would of course explain also the action of opium when it was directly injected into a vein.<sup>604</sup> Alexander Monro

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<sup>602</sup> Alston, C., Medical Essays and Observations,  
Edinburgh, 1742, V, 168.

<sup>603</sup> Kaau Boerhaave, A., Impetus Faciens ... Lugduni, 1745.  
see also Monro, A., Medical Essays and Observations,  
Edinburgh, 1771, 3, 299.

<sup>604</sup> See p. 164 et seq.

secundus attributed a greater importance to the process of absorption than Whytt. He demonstrated that substances were absorbed and distributed through the body by the circulation. His theory of action. was, however, based on action through the nerves, so that, although he knew absorption took place, he explained the subsequent effects by saying the absorbed medicines affected the nerves of the blood vessels and the heart.<sup>605</sup>

In the second half of the eighteenth century the doctrine of action directly through the nerves by poisons and highly active drugs was accepted by a majority of physicians. Among the dissentient voices was that of Haller, who did not believe that opium acted in this manner.<sup>606</sup> He supported his arguments by reference to some of the early experiments of Fontana, who was later to be one of the most outspoken opponents of the theory. The general opinion, however, favoured the doctrine which became so well established that the nineteenth-century toxicologist Robert Christison (1797-1882) wrote: "In the infancy of toxicology all poisons were believed to act through sympathy",<sup>607</sup> the word sympathy here

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<sup>605</sup> See p.183 et seq.

<sup>606</sup> Haller, A. von., Mémoires ... Lausanne, 1760, vol. 4, . . . p. 130.



meaning local impressions passing along the nerves from the site of administration to the organs secondarily affected.

The reason for the strength of the belief in action through the nerves was due to the support given to the arguments of Whytt, Monro and others by evidence pointing to the impossibility of rapidly acting substances exerting their effects via the circulation. This evidence was supplied by William and John Hunter who stated that the lymphatics were the only organs of absorption from the stomach and other parts. Until the Hunters announced their views on absorption, it was accepted that this process took place through both lacteals and veins. Haller held this belief and taught that water and aqueous fluids are absorbed by the 'pendulous' veins of the stomach. He stated further that such fluids are rapidly taken up by the veins of the intestine, whereas other matter entered through the lacteals.<sup>608</sup> In the winter of 1759-1760, William Hunter (1718-1783) in his lectures expressed the opinion that the veins do not absorb. He

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<sup>607</sup> Christison, R., A Treatise on Poisons, Edinburgh, 4th ed., 1845, p. 5.

<sup>608</sup> Hunter, W., Medical Commentaries, Part 1, London, 1762, p. 39.

published this statement in 1762, calling as evidence some experiments of his brother John (1728-1793), who had made observations on isolated portions of intestines in living sheep, a dog and an ass. In these experiments he noted that warm milk and starch solution injected into the isolated gut were absorbed by the lacteals, but he was unable to find any evidence of their being absorbed into the veins.<sup>609</sup> This work formed part of the Hunters' great contribution to the knowledge of the lymphatic system, but their denial of the absorptive powers of the veins had an unfortunate influence on pharmacology. By throwing doubt on this method of direct absorption into the circulation through the wall of the vein, they added support to the arguments in favour of a direct action upon

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<sup>609</sup> Hunter, W., Medical Commentaries, Part 1, London, 1762, pp. 42-52. Note. John Hunter was not the first to perform this experiment. Martin Lister in 1682 observed the uptake of an injected indigo solution by the lacteals in the intestine of a living dog (Phil. Trans., 1682, 13, 9). William Musgrave made the same experiment, injecting indigo solution into the jejunum of a dog and noting the appearance of a blue colour in the lacteals and ductus thoracicus (Phil. Trans., 1701, 22, 996). Neither of these workers, however, concerned ~~them~~ <sup>himself</sup> ~~selves~~ with absorption by the vein.

the nerves. One of the principal arguments in favour of action through the nerves was the rapidity with which certain substances acted after administration. Now it was stated, on the authority of the Hunter brothers, that a drug absorbed from the stomach had first to traverse part of the lymphatic system before being discharged into the blood. How, therefore, could a mode of action that was based on a preliminary absorption and entry into the circulation be reconciled with the rapid onset of the effects of opium or cherry-laurel?

Confirmation of this attitude is to be found in the writings of William Cullen, whose teaching had a considerable influence on the medical thought of his day. He believed that certain drugs were taken into the blood and distributed by the circulation and he gives this as the explanation for the action of the mercury salts. When, however, he comes to the rapidly acting substances, such as opium and cherry-laurel water, he is forced to adopt the alternative explanation. He states that opium acts upon the nerves because:

".... it produces its effects .... while it is yet in the stomach, and before it can be supposed to have reached the mass of the blood."<sup>610</sup>

The principal opponent at this time to this theory of direct action through the nerves was Felice Fontana. During the course of his many experiments he had shown that neither opium, Ticunas arrow-poison, cherry-laurel water or viper venom, brought about their toxic effects when immediately applied to the bared sciatic nerve. Furthermore, he showed that in the case of the venom a short period of time elapsed between the administration of the poison and the onset of its effects, so that these were not 'instantaneous' as so often claimed. These facts he considered to present experimental proof contrary to the theory of direct action through the nerves. In his discussion of opium, which he believed to act only after absorption, he answered the arguments which had been put forward in support of the nerve theory.

The argument which suggested that such extensive activity could not possibly arise from such a small dose he opposed, by saying, that it is no less remarkable to suggest that such a dose affects the mass of the nerves than to say that it effects the mass of the blood.<sup>611</sup>

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<sup>610</sup> Cullen, W., Treatise of the Materia Medica, Edinburgh, 1789, vol. ii, p. 231.

<sup>611</sup> Fontana, F., Traité, Florence, 1781, vol. ii, p. 365.

On the subject of the rapidity of action he points out that opium, cherry-laurel and ~~T~~icunas were all known to act rapidly when directly injected into the blood vessels and here there could be no doubt but that it acted through the circulation.<sup>612</sup> This, of course, does not answer the real problem which was concerned with the time required for a drug to be absorbed from the stomach and passed into the blood. Those who believed in action through the nerves said that the effects following injection were due to direct action on nerves in the lining of the blood vessels, but on this point Fontana claimed that anatomists knew of no organs on the lining of the vessels that might be properly called nerves.<sup>613</sup>

Fontana went too far, however, in his opposition by eliminating the nerves entirely from a participation in bringing about the effects of drugs and poisons. His theory was that these substances acted directly upon the blood by affecting its 'living principle'. John Hunter who had been responsible for reviving the idea that the blood was a living fluid, later agreed with Fontana in his belief that the viper venom directly attacked the blood.<sup>614</sup>

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<sup>612</sup> Fontana, F., Traité, Florence, 1781, vol. ii, p. 364.

<sup>613</sup> Ibid., p. 362.

Hunter, however, unlike Fontana, did not extend this to all poisons; for example, he said that nux vomica, the arrow-poisons and other poisons that did not cause a local reaction in the parts to which they were administered acted through the nervous system.<sup>615</sup>

Many physicians regarded Fontana's explanation of direct action on the blood as being neither original or creditable. Samuel Crumpe described it as an antiquated belief<sup>616</sup> and Cullen suggested that Fontana was the only physiologist in Europe who could believe that sudden death from cherry-laurel water could be due to an "operation on the blood".<sup>617</sup> Although his own theories were not generally acceptable, it is true to say that Fontana did succeed in helping to restore a balance between explanations that concerned a consideration of the nerves and those that were concerned with absorption and the circulation. From time to time in his work he

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<sup>614</sup> Hunter, J., Lectures on the Principles of Surgery, (1786-7) in The Works of John Hunter, editor J.F. Palmer, London, 1837, vol. i, p. 614.

<sup>615</sup> Ibid., p. 163.

<sup>616</sup> Crumpe, S, An Inquiry into the Nature and Properties of Opium, London, 1793, p. 104.

<sup>617</sup> Cullen, W., Materia Medica, Edinburgh, 1789, vol. ii, p. 286.

attacked the contemporary opinions that all human condition and diseases are attributable to a particular condition of the nerves.<sup>618</sup> The importance of these criticisms did not go unrecognized as shown by the following extract from a contemporary review:

"Readers are recommended to read Fontana's Traité. It has of late been but too fashionable for physicians to attribute everything to the nerves, and to pay no regard whatever to the circulating fluids."<sup>619</sup>

In 1795 Philip Wilson put forward four propositions to resolve some of the contradictions concerning the mode of action of opium. The first in importance was that the drug is absorbed into the circulation and carried in the blood to the brain.<sup>620</sup> This was not a new explanation; it had already been put forward by Willis and others, but Wilson sought to demonstrate the fact by means of experiment. Unfortunately, these experiments were very artificial, involving direct injection into the heart and they were not concerned with what was now the main problem relating to the mode of action of drugs.

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<sup>618</sup> Fontana, F., Traité, Florence, 1781, vol. ii,  
pp. 119, 135.

<sup>619</sup> Medical Commentaries, Edinburgh, 1787, 2, 117.

<sup>620</sup> See p. 293.

The paramount problem facing those who believed in an action through the circulation was to reconcile the speed of action of certain drugs and poisons with the process of absorption. It was no longer necessary merely to show that opium could reach the brain from the heart; it had to be demonstrated that it could reach the brain from the stomach or other point of administration in the short time between administration and the first observable effects.

The explanation that drugs acted by the process of absorption and transport in the blood became more improbable in the early years of the nineteenth century, when certain active constituents were isolated and their almost instantaneous effects demonstrated. The extraordinary rapidity of the action of hydrocyanic acid was reported in 1802 by Schrader<sup>621</sup> who described its effects on birds and by Emmert<sup>622</sup> in 1805 who reported effects on dogs. In 1814 Robert<sup>623</sup> reported that a rabbit given a dose of the acid died in a second and that a dog given a coffee-spoonful died instantly. In 1817 Magendie described

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<sup>621</sup> Schrader, J.C.C., Journal de Physique, de Chimie et d'Histoire Naturelle, 1802, 56, 225.

<sup>622</sup> Emmert, C.F., Diss.inaug.medica de venenatis acidi borussici in animalia effectibus, Tübingae, 1805. .

<sup>623</sup> Robert, Ann.Chim., 1814, 92, 62; Reported also in London Medical Repository, 1815, III, 246.



the acid as the quickest acting substance known and stated that an animal injected with it died "comme s'il eût été frappe d'un boulet ou de la foudre".<sup>624</sup> Similar results were demonstrated for other substances. In 1811 Benjamin Brodie, in a paper reporting experiments with vegetable or mineral poisons, described how essential oil of bitter almonds was placed on the ~~top of~~<sup>tongue</sup> of a cat, which was instantly seized with violent convulsions,<sup>625</sup> and similar results occurred with empyreumatic oil of tobacco (obtained by destructive distillation of tobacco leaves).<sup>626</sup> Certain of the newly isolated alkaloids were also shown to be very swift in their action; for example, Pelletier and Caventou<sup>627</sup> demonstrated that strychnine acted within a minute after administration into a wound.

To the majority direct action through the nerves appeared to be the only possible and indeed the only rational explanation of the mode of action of these rapidly acting drugs and poisons. It was generally accepted that this was physiologically possible and it was deemed to be proved by the well-known effects of belladonna

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<sup>624</sup> Magendie, F., Ann.Chim.Phys., 1817, 6, 349

<sup>625</sup> Brodie, B., Phil.Trans., 1811, 101, 184.

<sup>626</sup> Ibid., p. 191.

<sup>627</sup> Pelletier & Caventou, Ann.Chim.Phys., 1819, 10, 172.

extracts applied to the eyes.<sup>628</sup> At the time, however, this was a minor point and the arguments in favour of action through the nerves rested almost entirely upon the fact that it was not considered possible to reconcile such rapidity of action with an explanation that depended upon a preliminary absorption from the stomach. For these reasons, before the doctrine of action through the nerves could be seriously challenged, it was necessary to advance the knowledge of the physiology of absorption and the rate of circulation. Most important, and as a first step, it was necessary to prove the Hunters wrong and re-establish the fact of venous absorption. This was accomplished by the French physiologist François Magendie.

Magendie had obtained his degree of Doctor of Medicine in 1808 and not long after he drew attention to himself by criticising certain aspects of the vitalist theories that had been supported by the greatly respected Xavier Bichat (1771-1802).<sup>629</sup> About the same time with the assistance of a student, Alire Raffeneau Delille, he began to experiment with the Javanese arrow-poisons called Upas tieute and Upas antiar. These had been

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<sup>628</sup> Brodie, B., Phil. Trans., 1811, 101, 183.

<sup>629</sup> Magendie, F., Quelques idées générale sur les phénomènes particuliers aux corps vivans, Bull.d.Sc. med. de la Soc.méd.d'émulation, 1809, 4, 145.

brought to France by the naturalist Leschenault de la Tour (1773-1826), who also brought specimens of the plants from which the poisons were prepared, these being identified later as of the Strychnos genus.

The results of the experiments were published by Magendie and Delille in 1809 in a series of three papers, which are of considerable importance in the history of pharmacology. In them the authors (i) described the effects of arrow-poisons, (ii) discovered the sites of action, (iii) related the observed effects to those of other known poisons, (iv) demonstrated that the action of the poisons followed absorption and transport in the circulation, and (v) questioned Hunter's belief (which had been supported by Bichat) that the veins do not absorb.

Two of the three papers were principally concerned with the arrow-poisons. The first of these was read before the Académie des Sciences by Magendie on 24 April 1809. The memoir was entitled 'Examen de l'action de quelques végétaux sur la moelle épinière'<sup>630</sup> and this was reported with particular reference to the Upas tieuté in the Bulletin of the Société philomatique de Paris under

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<sup>630</sup> See Procès-Verbaux des Séances de L'Académie, 1808-1811. Hendaye, 1913, Vol. 4, pp. 196, 208.

the title "Des Effets de l'Upas Tienté (sic) sur l'économie animale".<sup>631</sup> The work reported in this paper formed the basis for Delille's doctoral thesis which was published in 1809 under the title 'Dissertation sur les Effets d'un Poison de Java, appelé Upas Tieuté, et sur la Noix vomique, la Feve de St. -Ignace, le Strychnos potatorum, et la Pomme de Vontac, qui sont di du même genre des plantes que l'Upas tieuté', Paris, 1809.

The second of the two papers on the Upas poisons was delivered by Delille on 28 August 1809. It was entitled "Examen des Effets de l'Upas antiar et de plusieurs substances emetiques".<sup>632</sup> A characteristic feature of the poisoning by Upas antiar was a violent vomiting, and in this paper the action of the arrow-poison is compared to other emetics in particular to the Tarter emetic.<sup>633</sup> Both of these papers on the arrow-poisons

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<sup>631</sup> Magendie & Delille, Nouveau Bulletin des Sciences par la Société philomatique, 1809, Vol. I (No.22), 568.

<sup>632</sup> See Procès-Verb. Acad. d. Sci., 1808-1811, Hendaye, 1913, Vol. 4, pp. 242, 275.

<sup>633</sup> Note. This was the first of several papers on emetic drugs and the physiology of vomiting with which Magendie was associated. In the years that followed he continued to be interested in this subject and notable contributions are:

were well received by the committee of the Académie, which had been set up to report on them.<sup>634</sup>

In their first experiment with the Upas tieuté Magendie and Delille administered the poison on a sharp sliver of wood, thrusting it into the thigh of a dog in imitation of its use as an arrow poison. Within three minutes all the muscles of the animal were seized with a violent convulsion, which passed off for a short period before giving rise to a further seizure affecting the breathing of the animal. Death occurred after five minutes and was due to asphyxiation which resulted from the poison affecting the muscles of the chest. The same experiment was carried out on other dogs, a horse and rabbits, always

"Vomissement," Procès-verb.Acad.d.Sci., 1813, Vol. 5,  
pp. 152-174.

"L'influence de l'émétique sur l'homme et sur les animaux," ibid., p. 244.

"L'action de l'oesophage," ibid., pp. 252, 447.

Reference has already been made to his work with Pelletier on emetine.

<sup>634</sup> For reports see Procès-verb.Acad.d.Sci., 1809, Hedaye, 1913, Vol. 4, pp. 208, 275. Members of the Committees were:

- (i) M.M. Sabatier, Pinel de Jussieu, Mirbel, Labillardière;
- (ii) M.M. Sabatier, Cuvier, Portal, Pelletan, Pinel.

with the same results.<sup>635</sup> In these experiments the brain appeared to be unaffected, so that the animal remained conscious during its agonies. The authors concluded that the site of action must be the spinal cord and to demonstrate this they made the following experiments.<sup>636</sup> They injected the poison into the thigh of a dog and then cut the spinal cord at a point between the occipital and first cervical vertebra. The convulsion took place as in the previous experiment. They then injected the poison into the pleura and disorganized the spinal cord by thrusting a piece of whalebone along its length. In this experiment the convulsion did not occur. To demonstrate further that the spinal cord was the site of action, they injected the poison into the peritoneum and, when the convulsions were well marked, they passed the whalebone slowly down the spinal column. The convulsions stopped, first in the fore-part of the body and then in the hind part as the probe destroyed the lower reaches of the cord. This suggested that the effect of the poison could be localized and Magendie and Delille made some experiments

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<sup>635</sup> Magendie & Delille, Nouv. Bull. Soc. Philomat., 1809, i, 368-9.

<sup>636</sup> Ibid., pp. 370-371.

applying the poison to different parts of the spinal cord. When placed on the lumbar region, the tetanus convulsions affected only the lower part of the body, but if placed on the cervical region, then the pectoral muscles and the fore limbs were affected.

These effects were produced by 2 to 3 centigrammes of the Upas poison, and the authors went on to show that similar doses of extracts of nux vomica and St. Ignatius's Bean produced the same results. Nine years later it was to be shown that these effects were due to the common constituent strychnine.

The determination of the site of action of the Upas tieuté was of great importance to the pharmacology of the strychnine-containing poisons, but its importance to pharmacology in general is due principally to the conclusions that the authors drew concerning the manner in which the poison reached the spinal cord. Here were all the factors in support for action through the nerves: it acted rapidly on the whole body in small doses and had been shown to produce its effects when applied to the nerve tissue in the spinal cord. In spite of this Magendie and Delille did not turn to this explanation. Instead they suspected that it was first absorbed and carried in the blood to the tissues of the spine. This was because

they were able to demonstrate that the action of the poison, although always the same, varied in its time of onset according to the manner in which it had been administered.<sup>637</sup> When injected into the peritoneum, the effects occurred within 20 seconds, but 5 minutes elapsed when the poison was injected into the small intestine. Again, action was rapid when the substance was placed in a wound, but much slower when inserted into the natural cavities of the body, e.g., the vagina. Finally, the onset of effects was prolonged considerably when the poison was given in the food. The authors attributed these differences to the time necessary for the poison to be absorbed from the site of administration and its transport in the blood to the spinal cord.

These conclusions led Magendie to consider the actual physiological process of absorption and one of the three papers read in 1809 reports the experiments he made concerning this important topic. The paper was read before the Académie on 7 August 1809 (second of the three in order of presentation) under the title "Mémoire sur les organes de l'absorption chez les mammifères".<sup>638</sup>

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<sup>637</sup> Magendie & Delille, Nouv.Bull.Soc.Philomat., 1809, i, p. 370.

<sup>638</sup> The paper was published in pamphlet form in Paris



Magendie began by referring to the rapidity with which the Upas tieuté acts and he thus acknowledged the principal argument in favour of a direct action through the nerves. In this work, however, because of his conviction that the poison is absorbed, he was less concerned with the nerves than with the lymphatics. He wrote:

"The ideas generally received concerning the organs of absorption leave no doubt that the lymphatic vessels are the agents which convey the poison into the blood circulation. Thus in the experiment where the poison is introduced into a wound in the thigh of an animal; we must admit it is taken up from the wound by the lymphatic vessels of the parts with which it was in contact ....."<sup>639</sup>

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in 1809 and there is a copy in the British Museum. It was reprinted in 1821 in Magendie's Journal de Physiologie expérimentale (1821, i, 18).

<sup>639</sup> Magendie, F., J.de physiol.expér., 1821,i,18):

"Les idées généralement reçues touchant les organes de l'absorption, ne permettent point de douter que les vaisseaux lymphatiques ne soient les agens du transport de ces poisons dans le système de la circulation sanguine. Ainsi dans l'expérience ou le poison a été introduit au milieu de la cuisse d'un animal, il n'y avoit pas deux manieres d'expliquer

But Magendie knew that to admit this meant that one believed the Upas poison to have entered the lymphatics, passed to the inguinal glands and thence via the lymphatics to the thoracic duct, where it ~~is~~<sup>was</sup> eventually discharged into the circulation at that point where the duct meets the subclavian vein. Magendie's experiences with the Upas poison had thrown considerable doubt on this explanation and, although he claimed, perhaps for the sake of appearances, that he began his experiments to add a degree of certainty to the prevailing opinion, the paper he produced is concerned with proving venous rather than lymphatic absorption.

In the first experiment<sup>640</sup> he ligatured the thoracic duct in a dog so as to isolate the blood circulation from the lymphatic system. He then injected the Upas poison into the peritoneum. The effects of the poison were as quick and as violent as when the duct is free. The same experiment was carried out administering the poison into the stomach, pleura muscles and intestines. In each case the same results occurred.

Now, if in these experiments the poison had not

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son absorption; on devoit nécessairement croire qu'il étoit pris dans la plaie par les vaisseaux lymphatiques des parties avec lesquelles il se trouvoit en contact."

<sup>640</sup> Magendie, F., J. de physiol. expér., 1821, i, 22.

acted, it would have been conclusive evidence for the theory of lymphatic absorption. The reverse, however, is not true. The results of the experiments where the full effect of the poison were observed with the thoracic duct tied could not be given as conclusive proof against the lymphatics being the only organs of absorption or that the veins absorb. One reason was that others before Magendie had tied the thoracic duct to investigate absorption in the lymphatics and in most cases variable results had been obtained. Magendie himself quoted the experiments of Guillaume Dupuytren (1778-1835), who had tied the thoracic ducts in several horses. In these experiments some of the horses had died, but others survived. The main problem was that it had not been fully proved that the thoracic duct was the only route by which lymph and its absorbed substances entered the circulation. Shortly afterwards, for example, Everard Home and Benjamin Brodie reported experiments made in an attempt to prove that other routes existed.<sup>641</sup>

Magendie realized these difficulties and, therefore, turned to another means of removing the lymphatic 'bridge' between the site of administration and

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<sup>641</sup> Home, E., Phil.Trans., 1811, 101, 163.

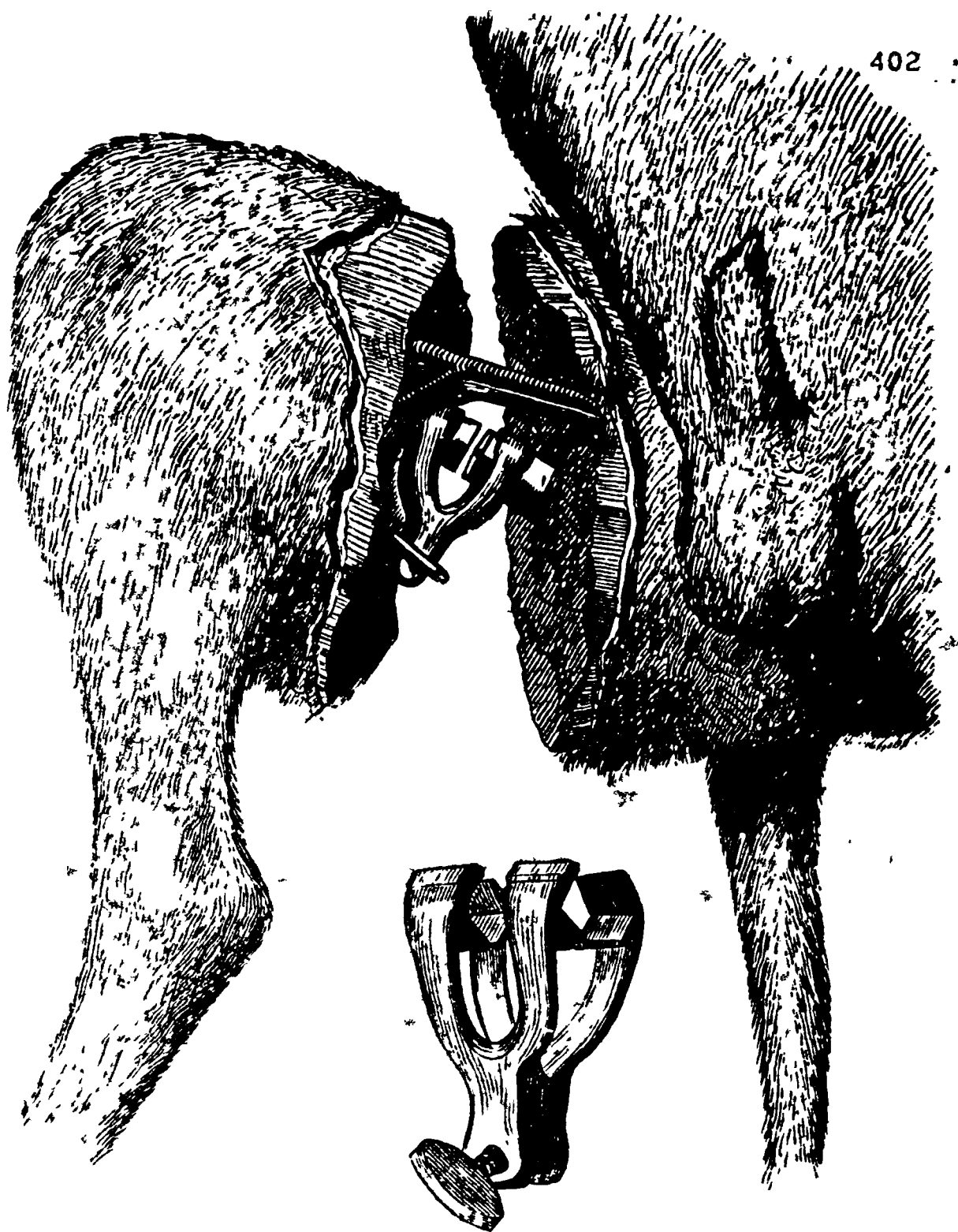
the circulation. He took as his subject a dog which had consumed a large meal seven hours previously, so that chyle would be clearly distinguished in the lymphatic vessels of the abdomen. He made an incision in the abdomen and withdrew a small portion of the small intestine to which he applied two ligatures spaced four decimetres (about 16 inches) apart. He then severed all vessels supplying the intestine between the ligatures and all blood vessels except for one vein and one artery. The remaining vessels were carefully scraped to remove all vestiges of lymphatic tissue and the portion of the intestines severed from the remainder just beyond the ligatures. The poison was injected into the isolated intestine which was then replaced in the abdomen. Within 6 minutes the characteristic symptoms of poisoning were evident. Post-mortem examination yielded no evidence that the ligatures had been displaced or that any of the poison had escaped into the abdominal cavity. This experiment was repeated several times and always with the same result. Magendie commented:

".... it [the experiment] proves as much as can be proved by physiology, that the lacteal vessels are not exclusively the organs of intestinal absorption."<sup>642</sup>

It was possible, however, that this situation might be peculiar to the intestine, and to determine if the same occurred in other parts of the body, Magendie made the following experiment using a technique similar to that used by Monro on frogs. The hind limb of a dog, which had been stupified with opium, was completely isolated from the trunk except for a connecting crural artery and vein. When the dissection was complete, 2 grains of the poison were inserted into the paw. The poison was found to exert its effects within four minutes and the animal was dead in ten. Later in the nineteenth century this experiment was repeated by Magendie's great pupil, Claude Bernard (1813-1878), who introduced a refined technique to prevent damage to the connecting vessels (see Plate VIII). Magendie introduced a modification into the experiment to eliminate the remote possibility that some lymphatic material may have adhered to the vessels and so transmitted the poison. He repeated the dissection but this time he introduced a quill into each of the connecting vessels,

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642 Magendie, F., J.de physiol.expér., 1821, i, 25:  
".... elle prouve, du moins autant que l'on peut  
prouver en physiologie, que les vaisseaux lactés ne  
sont point les organes exclusifs de l'absorption  
intestinale."



Disposition de l'expérience pour l'étude des voies de l'absorption (expérience de Magendie modifiée). — La forte pince double figurée à part sert à fixer le fémur qui est sectionné perpendiculairement.

Plate VIII. Bernard's modification of Magendie's experiment with the isolated limb.

secured them with ligatures and then divided the vessel between the two strings. Thus the blood was the only 'vital' connexion between the limb and the remainder of the body. The result was as before; shortly after the poison had been inserted into a wound in the isolated limb, the animal exhibited the characteristic convulsions.<sup>643</sup>

These experiments had definitely shown that the poison was transmitted in the blood from the limb to the body. There remained, however, the question of the actual organs of absorption. Magendie recognized two possibilities: absorption either by lymphatic capillaries which anastomose immediately with blood capillaries, or by the extremities of the veins. His own work suggested the latter and supported the opinion that the poisons were absorbed directly through the walls of the blood vessels.<sup>644</sup> By eliminating the process of lymphatic absorption Magendie sought to explain the rapidity of action of certain drugs and poisons.

"This new mode of absorption, much more direct than the lymphatic absorption, enables us to conceive the rapidity with which various deleterious

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<sup>643</sup> Magendie, F., J. de physiol.expér., 1821, 1, 26.

<sup>644</sup> Ibid., p. 27.

substances are absorbed and also the promptitude with which their effects are produced upon the system."<sup>645</sup>

The reception of this important paper was not particularly favourable. This does not surprise us, because it was unsatisfactory on two important points. First, it did not fully prove venous absorption; and second, Magendie failed to demonstrate that the poison is carried in the blood all the way to the spinal cord. The committee set up by the Académie, with Philippe Pinel (1755-1826) as Chairman,<sup>646</sup> delayed its report on the mémoire for nearly four years. When it eventually appeared in 1813,<sup>647</sup> it congratulated Magendie and Delille on their experimental work but did not confirm that the work had proved the process of venous absorption. Others were subsequently of the same opinion and a specific objection is to be found in a footnote contributed by Sir James Palmer (1804-1871) in an edition of

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<sup>645</sup> Magendie, F., J. de physiol.expér., 1821, i, 27:  
 "Ce nouveau mode d'absorption, beaucoup plus direct que l'absorption lymphatique, donne le moyen de concevoir facilement le rapidité avec laquelle les diverses matières délétères on autres sont absorbées, ainsi que la promptitude de la production de leurs effets dans l'économie."



John Hunter's works. Palmer points out that, in the experiment on the isolated leg, the poison was inserted into the paw and it could, therefore, be argued that it had entered the circulation via the open and divided veins and not by a process of absorption.<sup>648</sup>

In the light of these criticisms it should be noted that Magendie did not at this stage claim to have proved venous absorption, neither did he claim that he had proved the Hunters wrong. On this latter point, although he had many facts to oppose the doctrine that the lymphatics were the only organs of absorption, he would not say that it was wrong, but only that it was not admissible in all circumstances. Thus Magendie refused to go beyond the conclusion justified by the results of his experiments. Nevertheless, there can be no doubt that he was convinced in his own mind about venous absorption, and in the years that followed he made many experiments to prove the fact. Some of these were indirect, such as his attempts to demonstrate that certain birds and reptiles lacked lymphatic chyliiferous vessels connecting intestine with

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<sup>646</sup> Other members were Cuvier, Pelletan, Portal.

<sup>647</sup> See Procès-verb. Acad. d. Sci., 1813, Hedaye, 1914,  
Vol. 5, p. 142 et seq.

<sup>648</sup> The Works of John Hunter, London, 1837, vol. iv,  
p. 312 (footnote).

subclavian vein.<sup>649</sup> Others were more to the point and actually demonstrated the passage of substances through the wall of a vein. This work was reported in a mémoire addressed to the Academie in 1820 under the title "La mécanique de l'absorption chez les animaux a sang rouge et chaud."<sup>650</sup> In one of the experiments reported in this paper he took a puppy and exposed one of the jugular veins along its length, carefully freeing it from all surrounding tissues. He then placed a piece of board under the vein to isolate it from all other tissues. When this was accomplished, a drop of a thick extract of nux vomica was placed on the vein taking care to see that none touched the tissues. Within a few minutes the animal exhibited the characteristic symptoms of nux vomica poisoning. The same results occurred when the experiment was repeated on a grown dog and on rabbits.<sup>651</sup> Magendie in this paper was principally concerned with the exact nature of the process of absorption. He had already drawn attention, in his textbook on physiology,<sup>652</sup>

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649 Magendie, F., Nouv.Bull.Soc.Philom., 1819, pp. 135, 145.

650 Procès-Verb.Acad. d. Sci., 1820, 7, 109:  
Magendie, F., J.de physiol. expér., 1821, i, 1.

651 Ibid., pp. 9-11

652 Magendie, F., Précis Elémentaire de Physiologie,  
Paris, 1816-17, vol. ii, p. 162.

to the prevailing opinion that absorption was a purely 'vital' phenomenon involving a belief in such things as 'sensibility of the absorbent mouths' and 'insensible organic contractility of chyliiferous vessels'; and in this mémoire he suggested that the process of absorption was not 'vital', but purely physical. The crucial experiment to demonstrate this was as follows: he detached a portion of the external jugular vein of a dog, and freed it from all surrounding tissue; a glass tube was then attached to each end and warm water passed through tube and vein; the piece of venous tissue was then immersed in a bowl of slightly acid solution; after 5 to 6 minutes the water emerging from the glass tube was distinctly acid. Magendie concluded that absorption of the water in the bowl had taken place through the wall of the vein and, since this was detached from the body, the process must be a physical one, partly due in his opinion to the capillary attraction of the wall.<sup>653</sup> He then compared the result of this experiment with dead tissue with the result of the experiment cited above, where nux vomica was applied to the exposed vein of a living dog to demonstrate, contrary to vitalist theory, that the process was the

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<sup>653</sup> Magendie, F., J.de physiol. expér., 1821, i, 8.

same in both cases. Within a few years the physical laws governing this process which Magendie in his lectures called imbibition,<sup>654</sup> were discovered and established by René-Joachim Henri Dutrochet (1776-1847).<sup>655</sup>

The failure by Magendie to prove venous absorption fully is not the most unsatisfactory aspect of his paper of 1809, for he had succeeded in raising serious opposition to the Hunterian doctrine of absorption and had laid the foundation for a more definite series of experiments to confirm his belief. A far more unsatisfactory factor was his failure to demonstrate that the poison is carried in the blood from the site of administration to the site of action. This was serious, not because he did not try to demonstrate it, but because he tried and failed. Towards the end of the paper of 1809 on

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<sup>654</sup> See report of Magendie's lectures, Lancet, 1835, I, 53 et seq.

<sup>655</sup> Dutrochet, R.J.H., Ann.Chim.Phys., 1827, 35, 393; 1828, 37, 191; 1832, 49, 411; 1832, 51, 159; 1835, 60, 337. Note. Experiments on absorption were also carried out by Magendie's pupil, Michele Foderá (1792-1848), and it has been claimed that he discovered the laws of osmosis in 1822, some years before Dutrochet's publications. See Castiglioni, A., A History of Medicine, New York, 2nd ed., 1947, p. 693.

absorption, he observed that his experiments which indicated the possibility of venous absorption rendered it evident that the venous blood must contain the poison and carry it to the spinal cord. To demonstrate this he separated the thigh of a dog leaving it attached by only the vein and artery after the manner of the other experiments. He then administered the Upas tieuté into a wound in the paw of the isolated limb and transfused the blood from the crural vein into the jugular vein of a sound dog. He allowed the blood to transfuse for six minutes, which was the time necessary for the poison to act according to his previous experience. This time, however, no deleterious effects were observed in the second dog. In another experiment he allowed the blood to pass five minutes, and when, after that time, the second animal did not exhibit signs of poisoning, he allowed the blood to return to the circulation of the animal that had received the poison, which immediately showed signs that its spinal cord was affected.<sup>656</sup>

Thus Magendie failed to transfuse the poison into a healthy dog and the Committee in their report on the Memoir noted this to be a weakness in the arguments

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<sup>656</sup> Magendie, F., J. de Physiol. expér., 1821, i, 30-31.

for venous absorption.<sup>657</sup> The reason for the failure was explained some years later by Claude Bernard who observed that Magendie had not allowed the transfusion to go on for long enough.<sup>658</sup> The five to six minutes he had allowed were not adequate for the poison to build up in sufficient concentration in the blood of the second animal, which, it must be remembered, had not been weakened by an extensive dissection and haemorrhage.

Magendie on his part made no attempt to explain his failure. He merely recorded that the blood which, according to his theory, should contain a deadly poison could not be shown to produce symptoms of poisoning in a healthy animal. Because he failed to follow up this problem, his theory that drugs and poisons characterized by their rapid effect act after absorption into the veins and after being carried to the site of action remained a subject of considerable doubt. Some workers continued to oppose the idea, among them John Morgan (1797-1847) and Thomas Addison (1793-1860) who, in 1829, argued on the basis of an experiment demonstrating the rapidity of action of woorara (curare)<sup>659</sup> and the failure of a crossed-circulation

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<sup>657</sup> See Procès-verb. Acad. de Sci., 1813, 5, 146.

<sup>658</sup> Bernard, C., Leçons de Physiologie Operatoire, Paris, 1879, pp. 338 et seq.

experiment to transfuse poisoned blood from a poisoned to a sound animal.<sup>660</sup> Their results induced them to put forward once again the theory of Monro that, although a poison may be absorbed into the blood through the vein, the actual effects are produced by its action upon the nerves on the inner lining of the blood vessels.

There was now an accumulation of experimental 'evidence' for both theories with the result that, in the third decade of the nineteenth century in the lectures and in the text-books, action via the circulation and action via the nerves were put forward to explain the effects of drugs and poisons. Robert Christison<sup>661</sup> in his textbook of toxicology accepted the theory of absorption only in so far as it was proved that the poison entered the blood. To explain further, he spoke in favour of the Morgan-Addison theory, although it should be noted that he did not commit himself to it fully. Similarly the pharmacologist Jonathon Pereira (1804-1853)<sup>662</sup> in his lectures on the

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<sup>659</sup> Morgan & Addison, Essay on the Operation of Poisonous Agents on the Living Body, London, 1829, pp. 69, 71.

<sup>660</sup> Ibid., pp. 81-87.

<sup>661</sup> Christison, R., Treatise on Poisons, Edinburgh, 1829, 1st ed., p. 5 et seq.; 1832, 2nd ed., p. 5 et seq.

<sup>662</sup> Pereira, J., London Medical Gazette, 1836, 17, 38 et seq., Elements of the Materia Medica, London, 1839, 1st ed., vol. i, p. 27.

materia medica in 1835 and later in his textbook, although appearing to favour the ideas of Magendie concerning absorption observed that absolute proof is not available and he noted that the theory of action through the nerves was not improbable for the rapidly acting drugs.

A period of approximately ten years passed before Christison and Pereira admitted that drugs acted by absorption and transport in the blood and that the theory of action through the nerves was insecurely founded. This change of opinion was due to a number of factors which included the identification of poisons in the blood and in organs situated at a distance from the site of action (work in which the toxicologist Orfila was the principal contributor), and an increasing number of experiments on animals with poisons and drugs. These experiments included a critical evaluation of Morgan and Addison's theory by the surgeon, James Blake (1815-1895?),<sup>663</sup> work described by Pereira<sup>664</sup> as giving the coup-de-grâce to the theory of action through the nerves. The physiology of absorption

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<sup>663</sup> Blake, J., Fdinb.med.surg.J., 1839, 51, 330; 1840, 53, 35; 1841, 56, 412. See also Earles, M.P. M.Sc. dissertation, 1954, pp. 87 et seq.

<sup>664</sup> Pereira, J., Elements of the Materia Medica, 1849, 3rd ed., vol. i, p. 114.



of drugs and poisons and the mode of action of these substances was subsequently given confirmation by Claude Bernard, who reported and improved the techniques and experiments of Magendie. Bernard's work indicated that the demonstration of transportation of poisons in the blood was within the power of Magendie. Unfortunately Magendie had failed to demonstrate what he knew must be the truth and inexplicably left the whole question open.

Magendie's biographer, J.M.D. Olmsted, has described the three memoirs of 1809 as the beginning of experimental pharmacology and Magendie himself as the 'father' of the science.<sup>665</sup> Similarly, F.H. Garrison has described him as 'the modern founder of experimental pharmacology'.<sup>666</sup> These attributes are indeed justified, for in Magendie's studies of arrow poisons, prussic acid, alkaloids as well as in his Formulaire, we discern factors essential to an experimental and scientific pharmacology, i.e., a full recognition of the importance and value of animal experiment, an appreciation of dose and a study of the mode of action in relation to the mode of administration.

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<sup>665</sup> Olmsted, J.M.D., François Magendie, New York, 1944, p. 44.

<sup>666</sup> Garrison, F.H., An Introduction to the History of Medicine, London, 1929, p. 465.

Although the aim of this work was directed towards therapy or toxicology, it nevertheless forms a focal point in the history of what we have come to call experimental pharmacology, marking the end of one phase in that history and the beginning of another.

The method of animal experimentation was established and its importance recognized before Magendie. It was he, however, who broadcast and emphasized its importance in the progress of medicine. In the preface of his widely read Formulaire, he made it plain that the properties of the new medicines described therein had been determined in this manner. An example of his teaching on this subject is to be found in his paper on Prussic acid where he writes:

"Physiological experiments, which are so important to the theory of medicine, are no less important to the practice and application of that science. They reveal the true value of substances whose long use in medicine has been based only upon hypothetical principles and yield more information on the mode of action of the really active substances so that it becomes easier to vary their effects and to remedy their disadvantages. Their greatest advantage is to assist the physician in the discovery of new

medicaments either from amongst substances long known but not used in medicine or from the many simple and compound chemicals which are the daily discovery of modern chemistry and which, if subjected to the new methods of examination, may become particularly valuable to science and mankind." 667

Indirect evidence of Magendie's contribution to establishing the importance of animal experiment in the

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667 Magendie, F., Ann.Chim.Phys., 1817, 6, 347:

"Les expériences physiologiques, si nécessaires à la théorie de la médecine, ne sont pas moins importantes pour la pratique on les applications de cette science; par leur secours, une grande nombre de substances employées depuis long-temps comme médicamens, d'après des idées hypothétiques, sont appréciées à leur juste valeur. Les remèdes réellement actifs sont mieux connus quant à leur mode d'agir; il devient plus facile d'en faire varier les effets et de remédier à leurs inconveniens; mais le principal avantage de ces expériences, c'est le tenir le médecin toujours sur la voie de découvrir de nouveaux médicamens, soit qu'il le prenne entre les substances anciennement connues, mais non encore usitées en médecine, soit qu'il le trouve parmi cette foule de corps simples ou composés que la chimie nous révèle chaque jour, et qui, soumis à ces nouveau genre d'examen, peuvent devenir à-la-fois utiles à la science et à la humanité."

field of physiology and pharmacology is to be found in the opinions of the nineteenth-century anti-vivisectionists; for, although hundreds of animal experiments had been carried out before Magendie's time, it was his name that for a time became notorious in connexion with vivisection.<sup>668</sup> On this matter it is worthy of note that the literature indicates that Magendie and some of his predecessors were not oblivious or entirely unsympathetic to the suffering caused by their experiments. Haller speaks of his experiments on irritability as a species of cruelty, for which he felt a reluctance overcome only by the desire to benefit mankind.<sup>669</sup> Fontana, in order to explain why he carried out so few experiments with viper venom on dogs and cats noted that the subject did not justify the suffering caused.<sup>670</sup> Magendie in one of his experiments on the isolated limb gave the dog opium "afin de lui éviter la douleur d'une expérience difficile".<sup>671</sup> It cannot be denied that the experiments carried out by these three men

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<sup>668</sup> See Olmsted, J.M.D., François Magendie, New York, 1944, pp. 138 et seq.

<sup>669</sup> Haller, A., von., Comment.Soc.reg.Gottingae (1752), 1753, 2, 114.

<sup>670</sup> Fontana, F., Traité, Florence, 1781, vol.I, p.125.

<sup>671</sup> Magendie, F., J.de physiol.expér., 1821, I, 25.

were the cause of appalling suffering, but it would be wrong simply because of this to call their humanity into question. Certainly each conformed to Bernard's description of the dedicated physiologist and scientist:

"A physiologist ..... is a man of science, absorbed by the scientific idea which he pursues: he no longer hears the cry of animals, he no longer sees the blood that flows, he sees only his idea and perceives only organisms concealing problems which he intends to solve." <sup>672</sup>

Returning to the main theme it may be stated that reliance on experiment and recognition of the importance of dose would not be sufficient to support a claim that Magendie was the first 'modern' experimental pharmacologist. These factors had occurred in work before Magendie, and indeed some of the techniques that he used were modifications of earlier work. The real import of his work lies in his studies concerning the mode of action of drugs. He systematically administered related substances and showed that the effects were the same. He

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<sup>672</sup> Bernard, C., An Introduction to the Study of Experimental Medicine (1865), translated by H.C. Greene, 1949, p. 103.

then went further and demonstrated that these effects were due to an action at a specific site in the body. Later along with others he recognized that these effects were produced by active constituents in the drug or poison which could be extracted and administered in a chemically pure form. To this fact he gave full recognition in the Formulaire. He further showed that active substances were absorbed directly into the blood through the veins and, most importantly, that this was a physical and not a 'vital' process.

These facts taken as a whole indicate that many of the subsequent developments in modern experimental pharmacology may be traced to the work of Magendie. The many hundreds of systematic experimental studies of natural and synthetic drugs are but more sophisticated models of the pharmacodynamic studies of Magendie and his colleagues. The more recent studies of the localization of action of drugs and poisons are in a sequence of events that began with Magendie and Delille's studies of the strychnine poisons. Finally, the objective reports of Magendie foreshadow the development of the significant work of Rudolf Buchheim (1820-1879) and Oswald Schmiedeberg (1838-1921) of Dorpat, who freed pharmacology from traditional therapeutics and viewed drugs and other active substances according to their chemical and pharmacodynamic action rather than their therapeutic effects.

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